

UNITED STATES DISTRICT COURT

DISTRICT OF ARIZONA

In Re Bard IVC Filters Products
Liability Litigation

No. MD-15-02641-PHX-DGC

EXHIBIT INDEX

**PLAINTIFFS' SEPARATE STATEMENT
OF FACTS IN SUPPORT OF THEIR
OPPOSITION TO DEFENDANTS'
MOTION FOR SUMMARY JUDGMENT
REGARDING PREEMPTION**

Exhibit 1 Kessler Preemption Declaration

Exhibit 1.B - D Kessler Report 09-26-16 (Filed Under Seal)

Exhibit 1.C - 1st Supplemental Expert Report D Kessler (Filed Under Seal)

Exhibit 1.D - 2nd Supplemental Report D Kessler (Filed Under Seal)

Exhibit 2 Declaration of Ramon Lopez

Ex A Christine Brauer Expert Report 4-13-17 (Filed Under Seal)

Ex B Christopher Ganser 10-11-16 Deposition Excerpts

Ex C Flowchart

Ex D David Kessler MD 7-31-17 Deposition Excerpts

Ex E **BPV-17-01-00109956-109957** (SNF Letter 4-28-1995) (Filed Under Seal)

Ex F Robert Carr 6-6-17 Deposition Excerpts

Ex G **BPV-17-01-00262213** (FDA Letter 2-18-09 re G2 510k Submission)
(Filed Under Seal)

Ex H **BPVE-01-01525227** (Chart Showing Withdrawn Prophylactic Filter)
(Filed Under Seal)

Ex I Murray Asch 05-02-16 (19:1 Redacted)

1 Ex J **BPVEFILTER-01-01573378** (Denali Final Study Report)
(Filed Under Seal)

2 Ex K **BPV-17-01-00098737**-98738 (Phillips Trial Ex 945)

3 Ex L1 **BPV-17-01-00098020** (RF PowerPoint) (Filed Under Seal)

4

5 Ex L2 AKA Ex 54 Carr (Redacted)

6 Ex M **BPV-17-01-00072614** (6-12-88 SNF Meeting Minutes) (Filed Under Seal)

7 Ex N **BBA-00013699-13715**; BBA-00012802-12821 (10-26-06 & 08-28-06
8 Everest Med Mon) (Filed Under Seal)

9 Ex O **BBA-00013300-13309** (12-08-06 Everest Med Mon) (Filed Under Seal)

10 Ex P **BBA-00013151-13158** (12-20-06 Everest Med Mon) (Filed Under Seal)

11 Ex Q 11-18-16 MIL Austin

12 Ex R Robert Carr Exhibit Chart

13

14 Ex S BPV-DEP-00005665-5666

15 Ex T **BPV-17-01-00204231** (07-13-15 FDA 483 Letter) (Filed Under Seal)

16 Ex U FDA Guidance for Cardiovascular IVC Filter

17 Ex V **BPVE-01-00280224** (SNF Build Schedule) (Filed Under Seal)

18

19 Ex W BPVE-502d-00000013-19

20 Ex X BPVE-01-010119821-9825

21 Ex Y FDA Guidance for Contact Lens

22

23 Ex Z *Austin v. Bard* 1/30/17 Hearing Transcript

24

25

26

27

28

EXHIBIT 1

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7 *Co-Lead/Liaison Counsel for Plaintiffs*

8 UNITED STATES DISTRICT COURT

9 DISTRICT OF ARIZONA

10
11 In Re Bard IVC Filters Products
Liability Litigation

No. MD-15-02641-PHX-DGC

12 **DECLARATION OF DAVID KESSLER**

13
14 I, David Kessler, declare and state as follows:


15 1. I am over the age of 18 and the statements made below are true and correct
16 of my own personal knowledge, unless otherwise stated.

17 2. I am one of the experts retained by Plaintiffs in the *In Re Bard IVC Filters*
18 *Products Liability Litigation* case, No. MD-15-02641-PHX-DGC, pending in the District
19 of Arizona.

20 3. I previously authored reports in this case dated September 26, 2016, and
21 March 3, 2017.

22 4. As part of my work on this case, I have been asked to provide additional
23 opinions relating to certain facts and issues recently raised by Bard in connection with its
24 Motion for Summary Judgment re Preemption (Doc. 5396).

25 5. My supplemental report dated July 15, 2017, contains these additional
26 opinions, which I incorporate into this Declaration by reference. I also incorporate my
27 September 26, 2016, and March 3, 2017, reports into this Declaration by reference.
28

Pursuant to 28 U.S.C. Section 1746, I declare under penalty of perjury that the foregoing is true and correct. 

David Kessler

EXHIBIT 1.B

(Filed Under Seal)

EXHIBIT 1.C

(Filed Under Seal)

EXHIBIT 1.D

(Filed Under Seal)

EXHIBIT 2

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12 *Counsel for Plaintiffs*

13 UNITED STATES DISTRICT COURT

14 DISTRICT OF ARIZONA

15 In Re Bard IVC Filters Products
16 Liability Litigation

No. MD-15-02641-PHX-DGC

**DECLARATION OF RAMON ROSSI
LOPEZ IN OPPOSITION TO BARD'S
MOTION FOR SUMMARY
JUDGMENT REGARDING
PREEMPTION**

(Assigned to the Honorable David G.
Campbell)

21
22 I, Ramon Rossi Lopez, declare under penalty of perjury, pursuant to 28 U.S.C. §
23 1746, that the following is true and correct to the best of my knowledge and belief:

24 1. I am over 18 years of age and am competent to testify about the matters
25 contained herein. The statements contained herein are based on my personal knowledge
26 and upon the basis of the documents contained herein.

27 2. I am an attorney with Lopez McHugh LLP, and co-lead and liaison counsel
28 for Plaintiffs in this matter.

1 3. In the course of this litigation, Defendants retained Dr. Christine L. Brauer
2 as an expert witness. A true and correct copy of her report of April 13, 2017, is attached
3 hereto as **Exhibit A**. This report identifies her opinions and findings relevant to this
4 matter.

5 4. On October 11, 2016, the parties deposed Christopher D. Ganser. **Exhibit B**
6 hereto contains true and correct copies of pages excerpted from his deposition transcript.

7 5. In the course of this litigation, Defendants retained Donna Bea Tillman as
8 an expert witness. The document attached hereto as **Exhibit C** is a true and correct copy
9 of a page from a flowchart that was included in Donna Tillman's report as Exhibit AA.

10 6. On July 31, 2017, the parties deposed David Kessler. **Exhibit D** hereto
11 contains true and correct copies of pages excerpted from his deposition transcript.

12 7. Among the documents disclosed by Bard was a letter purported to be from
13 the Food and Drug Administration ("FDA"), dated April 28, 1995. This letter was
14 addressed to Mr. Jonathan S. Kahan at Hogan and Hartson. A true and correct copy of the
15 letter as disclosed by Bard to Plaintiffs is attached hereto as **Exhibit E**.

16 8. On June 6, 2017, Plaintiffs deposed Robert Carr, Jr.. **Exhibit F** hereto
17 contains true and correct copies of pages excerpted from his deposition transcript.

18 9. Among the documents disclosed by Bard was a letter purported to be from
19 FDA, dated February 18, 2009. This letter was addressed to Genevieve Balutowski at
20 C.R. Bard, Inc. A true and correct copy of the letter as disclosed by Bard to Plaintiffs is
21 attached hereto as **Exhibit G**.

22 10. Among the documents disclosed by Bard was a flow chart titled "BPV Filter
23 Product Line Cont." A true and correct copy of the chart as disclosed by Bard to Plaintiffs
24 is attached hereto as **Exhibit H**.

25 11. On May 2, 2016, the parties deposed Murray Asch. **Exhibit I** hereto
26 contains true and correct copies of pages excerpted from his deposition transcript.
27
28

1 12. Among the documents disclosed by Bard was the report for the Bard Denali
2 Filter Study. A true and correct copy of the Bard Denali Filter Study Final Study Report
3 as disclosed by Bard to Plaintiffs is attached hereto as **Exhibit J**.

4 13. The document attached hereto as **Exhibit K** is a true and correct copy of
5 Plaintiff's Exhibit 945 in the *Phillips v. Austin* trial. This document shows an e-mail from
6 Brian Barry to John Weiland dated May 2, 2005 with the subject "Competitive Filter
7 Data."

8 14. The documents attached hereto as **Exhibits L1 and L2** are true and correct
9 copies of documents Defendants disclosed to Plaintiffs following Mr. Carr's deposition.

10 15. Among the documents disclosed by Bard were meeting notes from a
11 meeting that took place on June 12, 1998. A true and correct copy of the notes as
12 disclosed by Bard to Plaintiffs is attached hereto as **Exhibit M**.

13 16. Among the documents disclosed by Bard were meeting notes from medical
14 monitor adjudication meetings that took place on Aug. 28, 2006, and on October 26, 2006.
15 A true and correct copy of the notes as disclosed by Bard to Plaintiffs is attached hereto as
16 **Exhibit N**.

17 17. Among the documents disclosed by Bard were meeting notes from a
18 medical monitor adjudication meeting that took place on December 8, 2006. A true and
19 correct copy of the notes as disclosed by Bard to Plaintiffs is attached hereto as **Exhibit**
20 **O**.

21 18. Among the documents disclosed by Bard were meeting notes from a
22 medical monitor adjudication meeting that took place on December 20, 2006. A true and
23 correct copy of the notes as disclosed by Bard to Plaintiffs is attached hereto as **Exhibit P**.

24 19. In *Austin v. Bard*, Case No. CACE-15-008373, Plaintiff filed a motion in
25 limine regarding FDA 510(k) clearance and the lack of FDA enforcement. A true and
26 correct copy of the first page of that motion is attached hereto as **Exhibit Q**.

1 20. Attached hereto as **Exhibit R** is a chart depicting Bard's exhibits by
2 category, as relates to Bard's communications with or about FDA contacts from 1999-
3 2016. This chart is a true and correct summary of Bard's exhibits.

4 21. Among the documents disclosed by Bard was an e-mail from Jason Greer
5 dated July 16, 2005. A true and correct copy of that email is attached hereto as **Exhibit S**.

6 22. Among the documents disclosed by Bard was a warning letter from the FDA
7 dated July 13, 2015. A true and correct copy of that document as disclosed by Bard is
8 attached hereto as **Exhibit T**.

9 23. Among the documents disclosed by Bard was the Guidance for
10 Cardiovascular Intravascular Filter 510(k), issued on November 26, 1999. A true and
11 correct copy of that document as disclosed by Bard is attached hereto as **Exhibit U**.

12 24. Among the documents disclosed by Bard is a spreadsheet titled SNF Build
13 Schedule 2120F. A true and correct copy of that document as disclosed by Bard is
14 attached hereto as **Exhibit V**.

15 25. Among the documents disclosed by Bard was the final report for the Bard
16 Denali Filter Study. A true and correct copy of the Bard Denali Filter Study Final Study
17 Report as disclosed by Bard to Plaintiffs is attached hereto as **Exhibit W**.

18 26. Among the documents disclosed by Bard was a Health Hazard Evaluation,
19 dated December 17, 2004. A true and correct copy of that document as disclosed by Bard
20 is attached hereto as **Exhibit X**.

21 27. Attached as **Exhibit Y** hereto is a true and correct copy of the Guidance for
22 Industry – Premarket Notification (510 (k)) Guidance Document for Contact Lens Care
23 Products set forth by the FDA on May 1, 1997.

24 28. On January 30, 2017, the parties in *Austin v. Bard*, Case No. CACE-15-
25 008373, appeared for a hearing. Attached as **Exhibit Z** hereto is a true and correct copy of
26 pages excerpted from the Transcript of Hearing Proceedings.

1 EXECUTED this 1st day of September, 2017.
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4 
5 _____
6 RAMON ROSSI LOPEZ
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Exhibit A

(Exhibit 2)

(Filed Under Seal)

EXHIBIT B

(Exhibit 2)

3 — — —
4

6 _____

9 OCTOBER 11, 2016

10
11 DO NOT DISCLOSE - SUBJECT TO FURTHER
12 CONFIDENTIALITY REVIEW

Videotaped deposition of CHRISTOPHER
D. GANSER, held at HILTON SHORT HILLS,
41 John F. Kennedy Parkway, Short Hills, New
Jersey, commencing at 9:32 a.m., before
Margaret M. Reihl, a Registered Professional
Reporter, Certified Realtime Reporter, and
Notary Public.

GOLKOW TECHNOLOGIES, INC.
23 877.370.3377 ph | 917.591.5672 fax
deps@golkow.com

1 Q. Have you ever read it?

2 A. No.

3 Q. Do you know you're featured throughout
4 the report?

5 MS. DALY: Object to the form.

6 BY MR. LOPEZ:

7 Q. No, I mean your name is in the report.
8 Wouldn't you want to see what Dr. Kessler, a
9 plaintiff's expert said about, you know, some of the
10 documents that you may have created or weighed in on?

11 MS. DALY: Object to the form.

12 THE WITNESS: I'm sure I will be
13 presented with certain documents from that
14 report with my name on it.

15 BY MR. LOPEZ:

16 Q. Okay. And you haven't seen any part of
17 the report?

18 A. I have not seen any part of the report.

19 Q. Sir, do you agree that when a device is
20 cleared to be marketed through the 510(k) process that
21 this does not reflect a determination by the FDA that
22 the device is safe and effective?

23 A. Yes.

24 Q. That a determination of substantial

1 equivalence is not equivalent to an approval by the FDA
2 of the device's safety and effectiveness; you agree
3 with that?

4 A. Could you repeat the question.

5 Q. Do you agree that a determination of
6 substantial equivalence is not equivalent to an
7 approval by the FDA of the device's safety and
8 effectiveness?

9 A. Yes.

10 Q. And would you also agree that
11 substantial equivalence determination does not in any
12 way denote official approval of the device and that any
13 representation conveying an impression of official
14 approval is misleading and constitutes misbranding?

15 MS. DALY: Object to the form, lack of
16 foundation.

17 THE WITNESS: I would agree.

18 BY MR. LOPEZ:

19 Q. Okay. The next document, we talked
20 about guidance documents and how part of your job was
21 to be familiar with certain guidance documents as they
22 related to devices.

23 Do you recall that?

24 A. Yes.

EXHIBIT C

(Exhibit 2)

Figure 1- 510(k) Flowchart

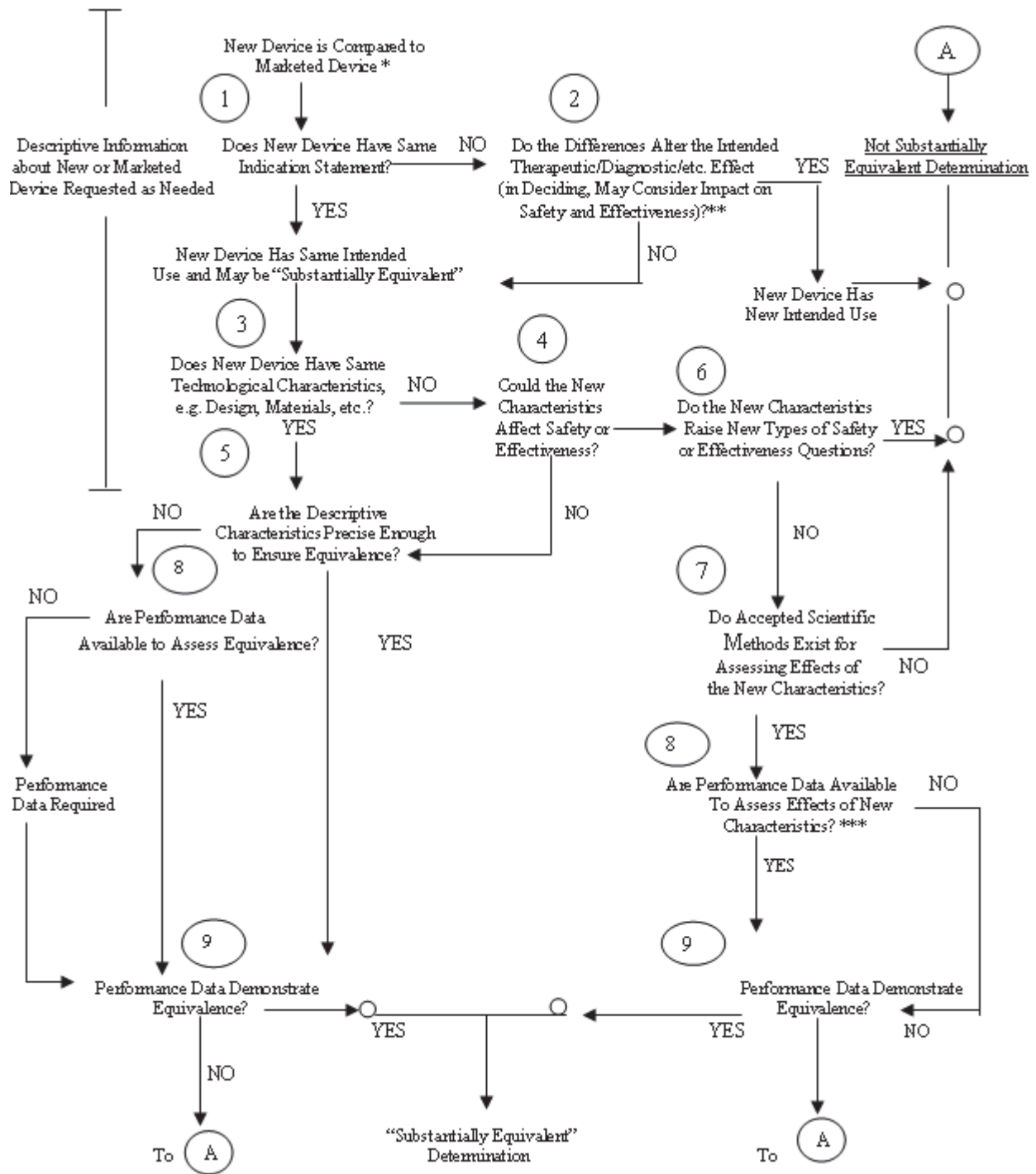


EXHIBIT D

(Exhibit 2)



Deposition of:
David Kessler , M.D.

July 31, 2017

In the Matter of:
**In Re: Bard IVC Filters Products
Liability**

Veritext Legal Solutions
1075 Peachtree St. NE , Suite 3625
Atlanta, GA, 30309
800.808.4958 | calendar-atl@veritext.com | 770.343.9696

In Re: Bard IVC Filters Products Liability

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1 BY MR. NORTH:

2 Q The 510(k) submission regarding Eclipse.

3 A Yeah, so it was in certain testing they felt
4 needed to further be done.

5 Q And what was the purpose of that further testing
6 they asked for?

7 MR. ARBITBLIT: Objection.

8 THE DEPONENT: So FDA was trying to get a handle
9 on these devices. It was like playing peekaboo.

10 BY MR. NORTH:

11 Q What do you mean they were trying to get a handle
12 on these devices?

13 A Well, so The FDA on Eclipse or on G2, for
14 example, FDA saw on Eclipse that the device had been
15 electropolished but questioned. If I believe my memory,
16 my memory serves me right, they had questions about the
17 validation and certain other testing, whether Bard had
18 done this. Similarly in G2 on Everest, you know, FDA
19 was concerned about adverse reaction reports from
20 Everest. So you see the agency constantly chasing the
21 company to try to get some sense of what's going on with
22 these devices because none of the 510Ks have the whole
23 story. They don't go to safety and effectiveness.

24 Q So was it your impression that in asking for more
25 information about Everest, that the agency was concerned

In Re: Bard IVC Filters Products Liability

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1 that these adverse events might pose some sort of safety
2 issue?

3 A I think the FDA was concerned why the company had
4 not reported adverse events. I'd have to pull the exact
5 letter. You see, for example -- I'll give you an
6 example. So take for example the question that FDA
7 asked where it said, "You reported that there had been
8 10 migrations." This is about Everest -- FDA is asking
9 this in one of the documents in Questions 3. "You
10 reported that there have been 10 migrations reported in
11 your hundred-patient study. This equates to an
12 incidence of migration of 10 percent. Please explain
13 why this rate of device migration is clinically
14 acceptable. In addition, please provide a comparison of
15 the approximate migration rates of the currently
16 marketed recovery and G2 filter devices based on your
17 clinical experience as compared to the investigational
18 recovery filter studied in the Everest trial."

19 And you see -- so FDA is concerned about this
20 10 percent. Nowhere does Bard in answering that say
21 that G2 failed caudal migration. Nowhere in response to
22 that question does Bard state that its medical monitor,
23 Dr. Kandarpa, raise significant concerns about the
24 Everest study and even questioned whether it should have
25 been stopped, and that the filter should be redesigned.

In Re: Bard IVC Filters Products Liability

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1 to death, correct?

2 A Yes.

3 Q Are you aware of any reports of a caudal
4 migration resulting in a catastrophic event leading to
5 death?

6 A So, I don't see that -- again, I don't think the
7 record informs me on that. I do know that Dr. -- I'm
8 not going to pronounce it right. I apologize. Dr. --
9 the medical director at Bard labeled those caudal
10 migrations critical in his analysis, but I don't have
11 specific data on deaths associated with caudal.

12 MR. NORTH: Move to strike as nonresponsive.

13 BY MR. NORTH:

14 Q Have you seen a report linking a caudal migration
15 with a catastrophic event and death?

16 A I have only seen -- the answer is no, but I have
17 seen Bard linking caudal migrations and labeling them as
18 critical in severity.

19 Q Do you have -- have you -- do you have an opinion
20 as to whether Bard filter's rate of tilt is higher than
21 that of competitive retrieval of filters?

22 MR. ARBITBLIT: Objection.

23 THE DEPONENT: We certainly have to go through
24 specifically each one. You certainly see, again, the
25 medical monitor in Everest becoming very concerned about

In Re: Bard IVC Filters Products Liability

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1 tilt and saying this is way too high compared to
2 anything in clinical practice -- in his clinical
3 practice.

4 BY MR. NORTH:

5 Q But have you formed an opinion as to whether the
6 tilt rate of Bard filters is higher than that of
7 competitive retrievable filters?

8 MR. ARBITBLIT: Objection.

9 THE DEPONENT: Yeah. Just give me one second per
10 se. I just want to check one thing in my report if I
11 can. Can you just repeat your question back? You're
12 talking about --

13 BY MR. NORTH:

14 Q Do you have an opinion as to whether the tilt
15 rate of Bard filters is higher than that of competitive
16 retrievable filters?

17 MR. ARBITBLIT: Objection.

18 THE DEPONENT: I think I go through in my report
19 specific filters, and I don't make a general statement.
20 I think mine tends to be device-specific. But just hold
21 on for one second. So certainly -- I don't -- I mean,
22 again, I think that tilt -- the medical monitor calls
23 out G2 and its tilt rate as being great. I think if you
24 look at the data in my report focuses primarily on
25 migration and fracture. But obviously the important

In Re: Bard IVC Filters Products Liability

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1 Q And if in reviewing a 510(k) application the FDA
2 wants the label changed, it can request it, correct?

3 A It's part of a negotiation with the company.
4 There's a back and forth.

5 Q And, in fact, for the G2 -- G2 filter, the FDA
6 requested a warning -- specific warning regarding the
7 use of the filter in morbidly obese patients, correct?

8 A I'd have to go back. I think there was a
9 request. I'd have to go back and actually understand
10 that chronology with regard to morbidly obese. I do
11 have it in my notes here.

12 Q Do you recall one way or the other whether a
13 warning regarding morbidly obese patients was ultimately
14 added to the G2 IFU?

15 A I have it here in my schedules exactly. Just let
16 me be -- I believe so. Happy to check. Just give me a
17 second and I can be double sure. Let me just see if I
18 can... I'd have to double-check on that to be sure. I
19 believe that's correct. But I think that there was a
20 back and forth with the company.

21 Q You haven't spoken with any of the actual
22 reviewers of Bard's 510(k)s, have you?

23 A I have not. I stayed with the record.

24 Q Are you going to offer any opinions that Bard, in
25 designing, manufacturing and selling any of its IVC

EXHIBIT E
(Exhibit 2)
(Filed Under Seal)

EXHIBIT F

(Exhibit 2)

1 IN THE UNITED STATES DISTRICT COURT

2 FOR THE DISTRICT OF ARIZONA

3

4 IN RE: BARD IVC FILTERS PRODUCTS)
LIABILITY LITIGATION) No.
5 _____) MD-15-02641-PHX-DGC

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10 DO NOT DISCLOSE - SUBJECT TO FURTHER
CONFIDENTIALITY REVIEW

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14 VIDEOTAPED DEPOSITION OF ROBERT MICHAEL CARR, JR.

15 Phoenix, Arizona

16 June 6, 2017

17 9:00 a.m.

18

19

20

21

22

23

REPORTED BY:

24 Robin L. B. Osterode, RPR, CSR

25 AZ Certified Reporter No. 50695

DO NOT DISCLOSE SUBJECT TO FURTHER CONFIDENTIALITY REVIEW

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1 certainly been revised.

2 Q. If I told you that there were no changes to
3 these four regulations from 2002 through 2013, other
4 than possibly formatting, would you have any reason
5 to disagree with that?

6 A. No, not without looking at them.

7 Q. Now, with respect to your work with --
8 there's reference in the last statute that I -- I'm
9 sorry, regulation that I showed you to three
10 additional types of requirements for filters. One is
11 ISO 10993. What is that requirement?

12 A. It's a requirement that outlines the
13 biocompatibility testing, biological testing that
14 medical devices, certain types of medical devices
15 must undergo.

16 Q. And when you say "certain types of medical
17 devices," that includes IVC filters. Correct?

18 A. It does.

19 Q. But there would potentially be other
20 medical devices that would also have to comply with
21 this ISO?

22 A. They do, to varying degrees, yes.

23 Q. Do you have any examples of other devices
24 besides IVC filters that would have to comply with
25 ISO 10993?

DO NOT DISCLOSE SUBJECT TO FURTHER CONFIDENTIALITY REVIEW

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1 A. I believe all do. But it depends on their
2 classification as to what testing you need to do.

3 **Q. So all devices have to establish**
4 **biocompatibility, but the testing that's needed to**
5 **establish, that will vary, depending on the type of**
6 **device. Fair?**

7 A. Yes. Context of the patient or it's an
8 implant, et cetera.

9 **Q. What's the 510(k) Sterility Review Guidance**
10 **and Revision of 2-12-90?**

11 A. It's pretty self-explanatory. It's a
12 guidance for testing for the sterility of a product.

13 **Q. Is that -- does that apply to all products?**

14 MR. NORTH: Objection to the form.

15 BY MR. CLARK:

16 **Q. I'm sorry, does that apply to all medical**
17 **devices?**

18 A. No.

19 **Q. Do you have an understanding of the types**
20 **of medical devices that this requirement applies to?**

21 A. Certainly implants. Those that are not --
22 some surgical tools that are usable it probably would
23 not apply to directly; it's a bit different. They
24 don't come sterile.

25 **Q. So that -- that requirement is essentially**

DO NOT DISCLOSE SUBJECT TO FURTHER CONFIDENTIALITY REVIEW

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1 dealing with ensuring that the device is not
2 presenting undue risk of infection. Correct?

3 A. That it's sterile, yes.

4 Q. And then the last one we have here is
5 Guidance for Cardiovascular/Intravascular Filter
6 510(k) Submissions. What is that requirement?

7 A. It's a guidance, not a requirement.

8 Q. Okay.

9 A. For the content that one should consider
10 submitting for 510(k) submission for vena cava
11 filters.

12 Q. Okay. So you made an important point
13 there. So we're talking about a guidance document
14 that is essentially the FDA's suggestions for what a
15 510(k) submission should include if you're trying to
16 get 510(k) clearance for an IVC filter?

17 A. Yes.

18 Q. Now, Class II medical devices, in general,
19 typically are devices that are used in connection
20 with a physician order. Correct?

21 A. Yes.

22 Q. They aren't things that a patient can just
23 go run out to a drug store and pick up off the
24 counter. Right?

25 A. No. Hopefully.

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1 testing that was performed in conformance with FDA
2 guidance document, Guidance for
3 Cardiovascular/Intravascular Filter 510(k)
4 Submission. And that's -- that guidance document is
5 the one we just talked about a few minutes ago.
6 Right?

7 A. It's an earlier version, I believe, but
8 yes, it is a guidance document.

9 Q. And what do you mean by "in conformance
10 with"? Do you mean by that that there's a
11 recommendation in this guidance document that bench
12 testing be performed, and therefore, BPV did bench
13 testing?

14 A. Yes. There are specific tests that they
15 request to be addressed.

16 Q. So the guidance document outlines a number
17 of tests that they recommend being done, and BPV did
18 those as part of its 510(k) submission?

19 A. Yes.

20 Q. You mention a number of times in your
21 declaration, and I'll just go through this generally,
22 that if Bard failed to respond to an FDA request
23 within 30 days, the submission would be withdrawn.
24 That's not a specific requirement for IVC filters, is
25 it?

DO NOT DISCLOSE SUBJECT TO FURTHER CONFIDENTIALITY REVIEW

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1 A. No, it's not.

2 Q. That's something that the FDA requires of
3 any manufacturer whose submission is found to be
4 deficient in any way, shape, or form?

5 A. In a particular kind of 510(k) submission.

6 Q. What kind of 510(k) submission?

7 A. In special 510(k)s. And sometimes the
8 length of time has changed, but --

9 Q. Okay. And that can be -- I think I saw one
10 of the exhibits in your declaration was a request for
11 additional time to provide a response. That request
12 can be granted on occasion. Correct?

13 A. It can be.

14 Q. On paragraph 10, in your declaration, page
15 6, there's a reference to an August 12, 2002
16 telephone conference between Impra and the FDA. Were
17 you a party to that telephone conference? You cite
18 Exhibit 8, if that refreshes your recollection.

19 A. I don't know if I was on the call or just
20 involved in answering the questions for sure.

21 Q. Okay. And I take it you didn't prepare the
22 document that's at Exhibit 8. Correct?

23 A. I didn't prepare it?

24 Q. You didn't write it?

25 A. No.

DO NOT DISCLOSE SUBJECT TO FURTHER CONFIDENTIALITY REVIEW

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1 indicate that the product has complied with other
2 aspects of federal law or the Food Drug and Cosmetic
3 Act. Correct? You've seen that language before?

4 A. Yes.

5 MR. CLARK: Let's take a short break.
6 We've been going for about an hour.

7 THE WITNESS: Okay.

8 THE VIDEOGRAPHER: Off the record. The
9 time is approximately 10:05 a.m.

10 (Recessed from 10:05 a.m. until 10:40 a.m.)

11 THE VIDEOGRAPHER: With the approval of
12 counsel, back on the record. The time is
13 approximately 10:40 a.m.

14 BY MR. CLARK:

15 Q. Sir, thank you for your patience during
16 that break.

17 A. No problem.

18 Q. I know that it was a long break, but I will
19 represent to you that it was time well spent since I
20 have eliminated about a third of my questions for
21 you.

22 A. Okay.

23 Q. So to follow up, I just want to make sure I
24 understand my notes on some of your prior testimony.

25 Now, there's -- there's nothing specific in

DO NOT DISCLOSE SUBJECT TO FURTHER CONFIDENTIALITY REVIEW

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1 the guidance documents -- strike that.

2 There's nothing in the guidance documents
3 that's specific to Bard filters. Correct?

4 A. No, it's a guidance for --

5 Q. Filter --

6 A. -- cardiovascular filters, yes.

7 Q. And it's not specific to retrievable
8 filters. Correct?

9 A. The testing that has been required is
10 specific to retrievable filters over permanent
11 filters.

12 Q. In the guidance document?

13 A. No.

14 Q. Okay. Then my question was about the
15 guidance document.

16 A. Yes.

17 Q. The guidance document has nothing specific
18 to retrievable filters. Right?

19 A. No.

20 Q. That's not right?

21 A. I'm sorry, no, it does not.

22 Q. Okay. Thank you.

23 Now, we've talked a lot about things that
24 were given to the FDA, and your declaration has 128
25 exhibits evidencing communications back and forth

DO NOT DISCLOSE SUBJECT TO FURTHER CONFIDENTIALITY REVIEW

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1 approximately 11:08 a.m.

2 BY MR. CLARK:

3 Q. Mr. Carr, before we went back on the
4 record, I asked you to see if you could locate in the
5 exhibits attached to your declaration documents you
6 believe indicate that the -- that Bard's
7 competitor -- competitive rate testing was provided
8 to the FDA. And you were kind enough to direct my
9 attention to Exhibit 35 to your declaration, page
10 BPV-17-01-00098580. And this describes, it looks
11 like, an oral communication between Shari Allen and
12 Charles Larson. Correct?

13 A. Yes. Excuse me.

14 Q. And in this document, Ms. Allen indicates
15 that she shared that "When comparative rates were
16 determined using the MAUDE database as a numerator
17 and IMS data as a sales denominator, the analysis
18 signaled that Recovery filter migration rates would
19 exceed those of competitive devices."

20 Did I read that correctly?

21 A. Yes.

22 Q. And then it goes on to say that "When
23 bariatric patients are removed from both the
24 numerator and the denominator, the migration rates
25 are within the range of competitive products."

DO NOT DISCLOSE SUBJECT TO FURTHER CONFIDENTIALITY REVIEW

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1 Correct?

2 A. Yes.

3 Q. Is this the document that you were
4 referring to earlier when you told me you believed
5 that the competitive test data had been shared with
6 the FDA?

7 A. It's one of them, yes.

8 Q. Okay. Now, this document itself describes
9 testing, but does not indicate that the actual data
10 from that testing was produced to the FDA.

11 Are you aware of any scenario where the
12 data from that testing was produced to the FDA?

13 A. I believe it's the one I referenced that
14 I -- I need to find.

15 Q. Okay. And there's potentially another
16 document out there that you believe you recall that
17 might indicate another communication with the FDA
18 where the competitive test data was provided to the
19 FDA?

20 A. Yes.

21 Q. Okay. And I talked with Mr. North before
22 we went back on the record. What we'll do is we will
23 mark as exhibit next, which I think was -- 9 --

24 THE REPORTER: 967.

25 BY MR. CLARK:

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1 **Q. -- 967?**

2 MR. O'CONNOR: Is the phone on?

3 THE WITNESS: Yes.

4 MR. O'CONNOR: Is it muted?

5 THE VIDEOGRAPHER: It's fine.

6 MR. O'CONNOR: Okay. Thank you.

7 BY MR. CLARK:

8 **Q. So Exhibit 967 will be attached -- will be**
9 **a holding place for this document, which if you can**
10 **locate it, you'll attach to your deposition. I trust**
11 **that you will be reading and signing your deposition.**
12 **If for some reason, I'm not suggesting your memory's**
13 **bad, but if it's not what you remembered it to be --**

14 A. Uh-huh.

15 **Q. -- and there is no such document, just make**
16 **a notation on a blank piece of paper that "I was**
17 **unable to locate any responsive document."**

18 A. Okay.

19 **Q. Is that fair?**

20 A. Yes.

21 (Marked for identification Exhibit 967.)

22 MR. CLARK: Sir, I would pass the witness
23 at this juncture.

24 THE WITNESS: Thank you.

25 MR. NORTH: I have no questions of this

EXHIBIT G

(Exhibit 2)

(Filed Under Seal)

EXHIBIT H

(Exhibit 2)

(Filed Under Seal)

EXHIBIT I

(Exhibit 2)

(Filed Under Seal)

1 IN THE UNITED STATES DISTRICT COURT

2 FOR THE DISTRICT OF ARIZONA

3

4 In Re Bard IVC Filters)

5 Products Liability Litigation)

6 -----) No. MD-15-02641-PHX-DGC

7

8 Do Not Disclose -

9 Subject to Further Confidentiality Review

10

11 This is the videotaped deposition of MURRAY R.

12 ASCH, M.D., taken before Terry Wood, CSR, RPR, a court

13 reporter, at Victoria Room, Residence Inn, 160

14 Consumers Drive, Whitby, Ontario, Canada, on the 2nd of

15 May, 2016, at 9:13 a.m..

16

17 Reported by: Terry Wood, CSR (Ont.), RPR

18 Videographer: Jim Lopez

19

20

21

22

23

24

1 [REDACTED]

2 Q. All right. Dr. Asch, I want to
3 talk to you now about that study.

4 What were you asked to do by Bard?

5 A. I was asked to recruit patients
6 into the study and assess the safety and feasibility of
7 both implanting the device, and removing the device to
8 ensure that it was -- it was safe and lived up to their
9 expectations of a retrievable device.

10 Q. And so part of the study was to see
11 if these could be taken out, in fact, after a period of
12 weeks?

13 A. Yes, the main --

14 MR. NORTH: Objection to the form. I'm
15 sorry.

16 BY MR. BOATMAN:

17 Q. And was part of your analysis as to
18 whether, in retrieval, the vein would be damaged in the
19 removal process?

20 MR. NORTH: Objection to form.

21 THE DEPONENT: Yes.

22 BY MR. BOATMAN:

23 Q. You can answer. When you say it
24 was -- would you call this a retrievability study?

1 A. Yes, absolutely.

2 Q. When you say a retrievability
3 study, is that different than a safety study?

4 A. Yes, there are different aspects of
5 any device and including an IVC filter. So an IVC
6 filter has a function to perform in terms of remaining
7 in position, in terms of protecting patients from
8 pulmonary emboli, blot clots to the lungs. However,
9 this study wasn't designed to test those things. This
10 study was designed to ensure that the device could be
11 safely removed.

12 Q. If you had been asked to do a
13 safety study for the use of the filter long-term, would
14 have the study been done differently?

15 A. Yes. There were different
16 questions. The study would have been done differently
17 with a different question.

18 Q. And give me some examples of how it
19 would have been done differently?

20 A. Well, the design of scientific
21 studies is a bit complex and challenging, depending
22 upon the specific questions. So if we are looking for
23 long-term safety of the device, I would then embark
24 upon a long-term study, leaving the filter in for a

EXHIBIT J

(Exhibit 2)

(Filed Under Seal)

EXHIBIT K

(Exhibit 2)

To: John Weiland

From: Brian Barry 

cc: Chris Ganser

Date: May 2, 2005

Re: Competitive Filter Data

As a follow up to questions asked by the Board on April 20th I re-reviewed the materials provided to FDA and have confirmed that we *did not* provide the competitive migration test data the Agency as I stated during the Board meeting. I apologize for my misstatement.

In reviewing what was provided, however, I confirmed that we did submit the comparative bench top migration test data for the original and modified Recovery Filters with the predicate Bard Simon Nitinol filter. The testing was done to a standardized protocol and, unlike the early testing done with competitive filters, used a statistically significant number of test devices. The comparative Recovery/Simon Nitinol Filter data was discussed in detail during our March 24th meeting with FDA and formed the basis for our discussions with them regarding the design improvements made to the modified filter which is currently undergoing 510(k) review.

I subsequently reviewed the advisability and need for providing FDA with the early competitive filter test results with our outside regulatory counsel, Mr. Howard Holstein of Hogan and Hartson, L.L.P. in Washington, DC. Howard agreed that the Recovery/Simon Nitinol comparison testing that we provided to FDA was both adequate and appropriate since the Simon Nitinol Filter was our declared predicate and comparative test device for the original Recovery Filter 510(k). Howard is also aware that we had provided FDA with our adverse event rates for the current recovery Filter, including migration, fracture and other rates as they compare with the SIR thresholds. Given the above, neither Howard nor I could think of any requirement or reason for us to share with FDA the initial directional migration testing done with competitive filters.

Please let me know if you need any additional information or would like me to provide an update to the Board.



50

Migration Resistance

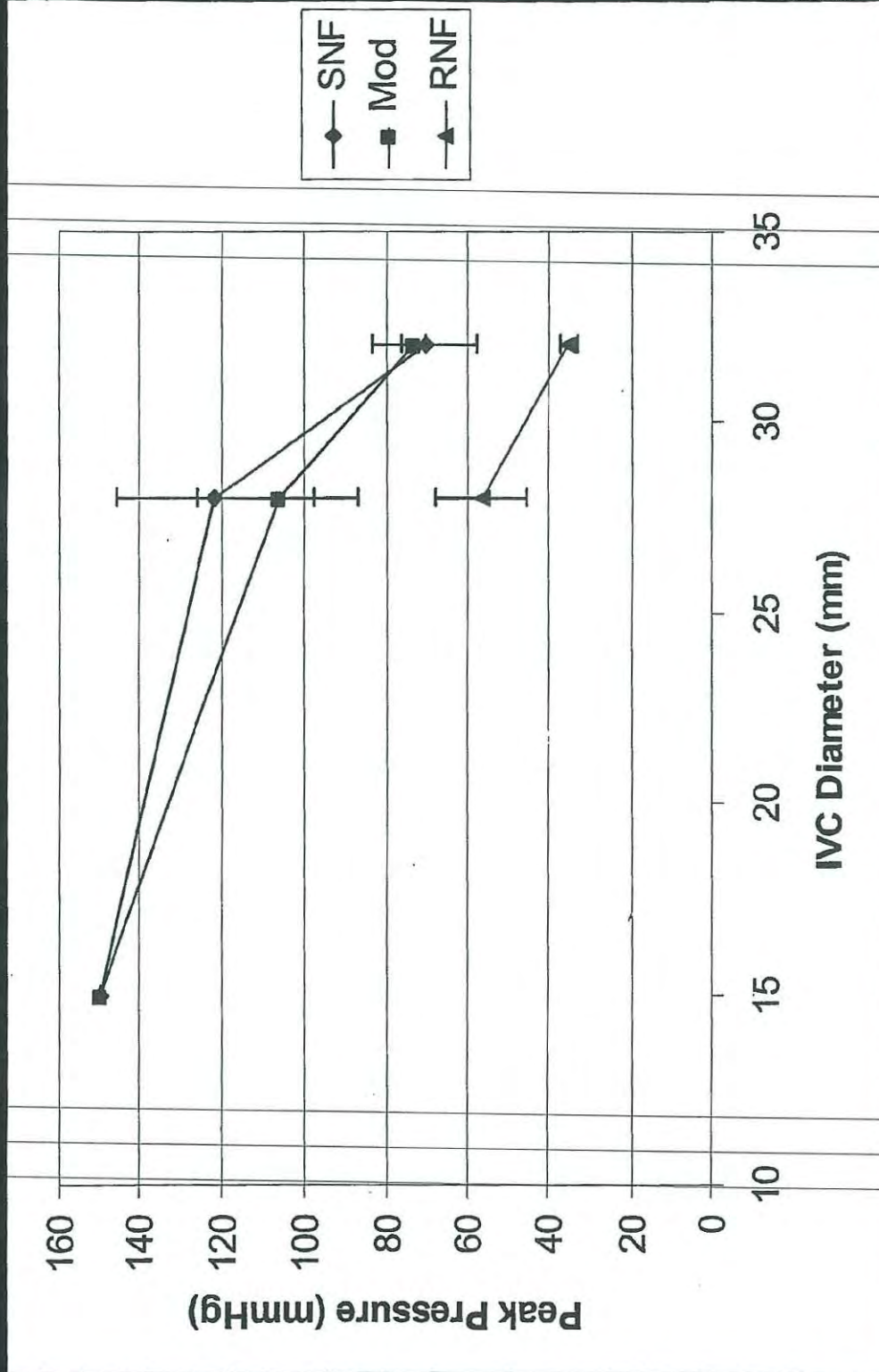


EXHIBIT L1

(Exhibit 2)

(Filed Under Seal)

EXHIBIT L2

(Exhibit 2)

Recovery® Filter System
Response to Questions (K050558)
June 3, 2005



CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER

CARR EXHIBIT 54, Page 1

BPV-17-01-00125416

Cover Letter

CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER

CARR EXHIBIT 54, Page 2

BPV-17-01-00125417



3 June 2005

Attn: Angela Smith
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
510(k) Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, MD 20850

Re: Response to Questions (K050558) - Recovery[®] Filter System

Dear Ms. Smith:

A Special 510(k) (K050558) was filed for the subject Recovery Filter System on March 2, 2005, and the Food and Drug Administration (FDA) requested additional information on March 30, 2005. In addition, a conference call (see Attachment A) was completed between Bard Peripheral Vascular, Inc. (BPV) and FDA on May 6, 2005. During the teleconference call, FDA indicated that they did not have enough data in the Special 510(k) to determine whether the modifications to the subject Recovery Filter System might affect the filter's long-term retrievability. FDA indicated that they would consider a proposal for acute retrieval up to 3-4 weeks, however, an indication for use change would require a traditional 510(k). During a subsequent telephone conversation on May 27, 2005, FDA indicated that an acute retrieval up to 3-4 weeks would not be accepted without clinical data. BPV intends to file an Investigational Device Exemption (IDE) to conduct a clinical study to assess the safety of the removal of the Recovery Filter.

In response to your March 30, 2005 request for additional information, BPV would like to request that the Special 510(k) (K050558) be converted to a Traditional 510(k) per the FDA Guidance for Industry, "Frequently Asked Questions on the New 510(k) Paradigm (October 22, 1998)." The information in this Traditional 510(k) is essentially identical (excluding format) to the Special 510(k) (K050558), with the following exceptions:

1625 West 3rd Street • P.O. Box 1740 • Tempe, AZ 85280-1740
Tel: 1-800-321-4254 • 1-480-894-9515 • Fax: 1-480-966-7062 • www.bardpv.com

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BPV-17-01-00125418



- **Catalog Number:** Changed from RF-210F to RF-310F.
- **Indications for Use:** Removed the last bullet point in the Indications for Use statement: "Recovery Filter may be removed according to the instructions supplied below under Section labeled: Optional Procedure for Filter Removal."
- **Instructions for Use:** A precaution was added to the Recovery Filter Removal section of the IFU, as follows: "The safety and effectiveness of the Recovery Filter for retrieval after 30 days has not been established." This precaution is identical to the precaution FDA required upon clearance of the predicate Recovery Filter System (K022236) on November 27, 2002. A statement was added to the Potential Complications section of the IFU: "There have been reports of complications, including death, associated with the use of the Recovery Filter System in morbidly obese patients." In addition, the removal procedure and clinical experience section of the IFU has been removed.
- **Predicate Device:** Removed all references to the Recovery Filter System with cleared with a removable indication (K031328).
- **Design Verification and Validation Testing and *In-Vivo* Non-Clinical Testing:** Included an updated diagram depicting the subject device animal study design. In addition, copies of the design verification/validation and *in-vivo* non-clinical testing protocols/reports are included on a CD-ROM.

C.R. Bard, Inc. has not publicly disclosed or acknowledged the fact of its intent to market this product to any individual outside its employ, other than disclosures made under commercial agreements containing appropriate safeguards for secrecy. As a result, C.R. Bard, Inc. requests that the FDA keep and maintain confidential both the existence and the contents of this Premarket Notification in accordance with 21 CFR 807.95(b). C.R. Bard, Inc. also requests that the FDA keep and maintain confidential the contents of this letter.

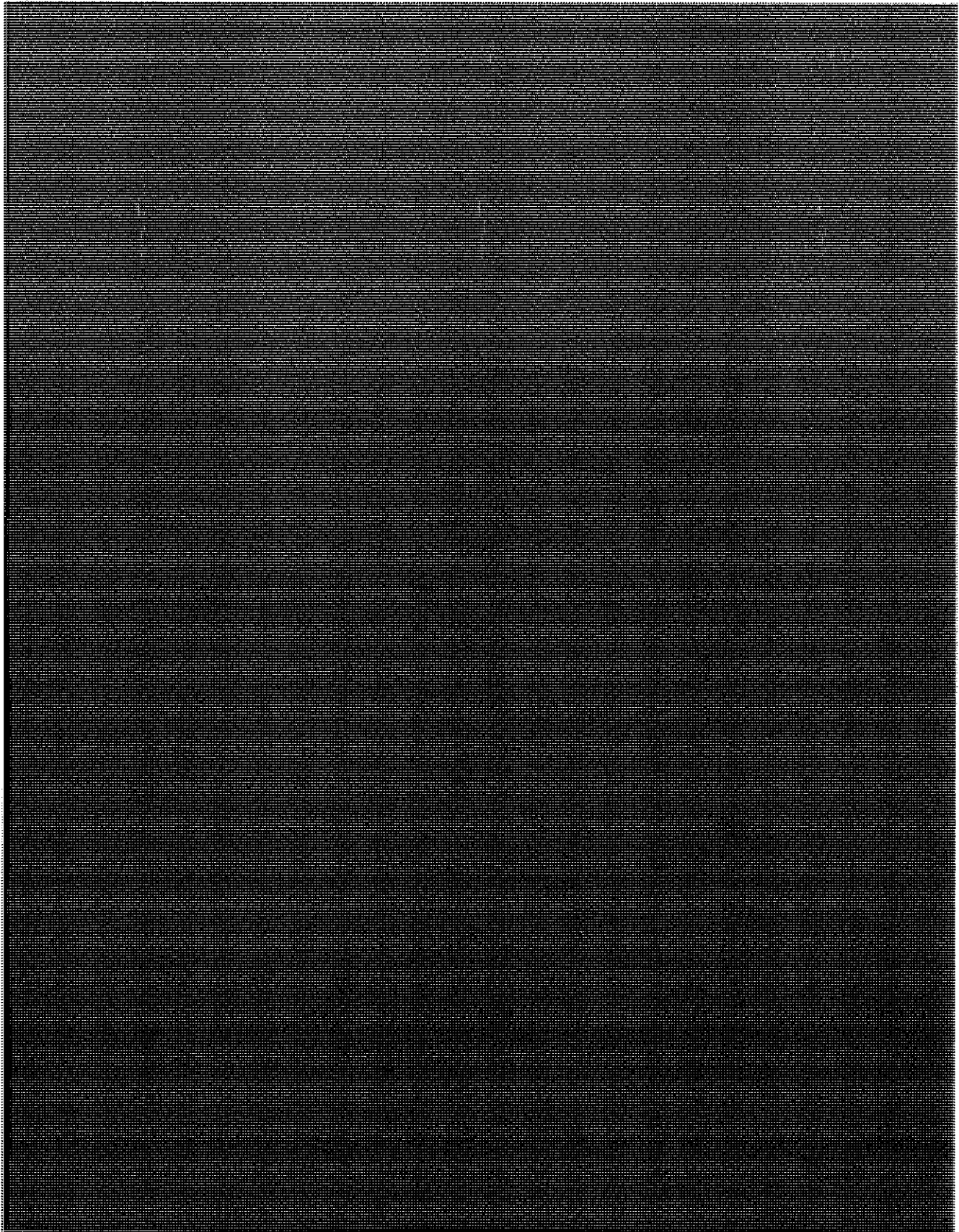


Thank you in advance for your expeditious consideration of this notification. You can contact me via telephone at 480-263-4817, fax at 480-449-2545, or e-mail at shari.allen@crbard.com.

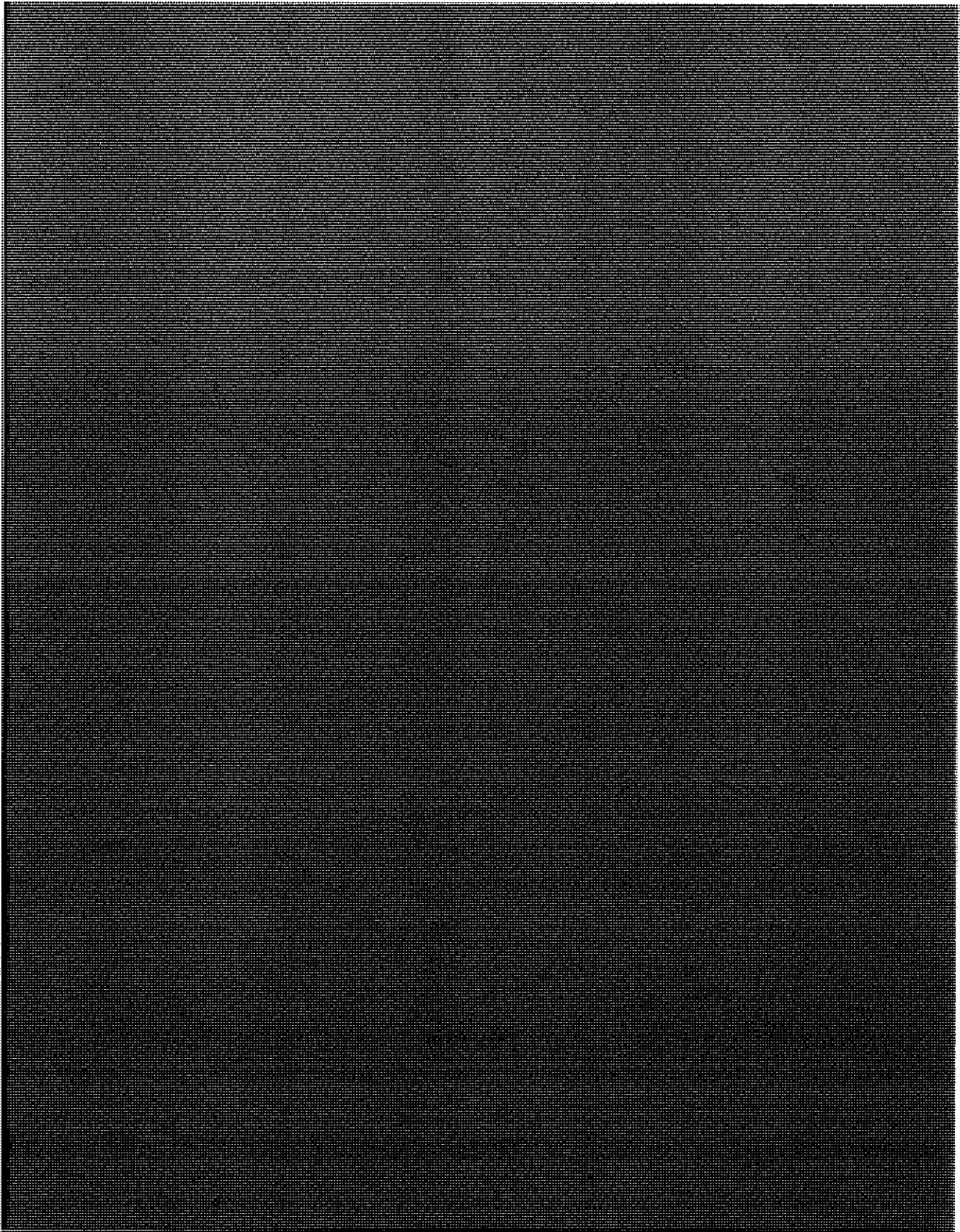
Sincerely,

A handwritten signature in cursive script, appearing to read "Shari Allen".

Shari Allen
Director, Regulatory Affairs and Clinical Research

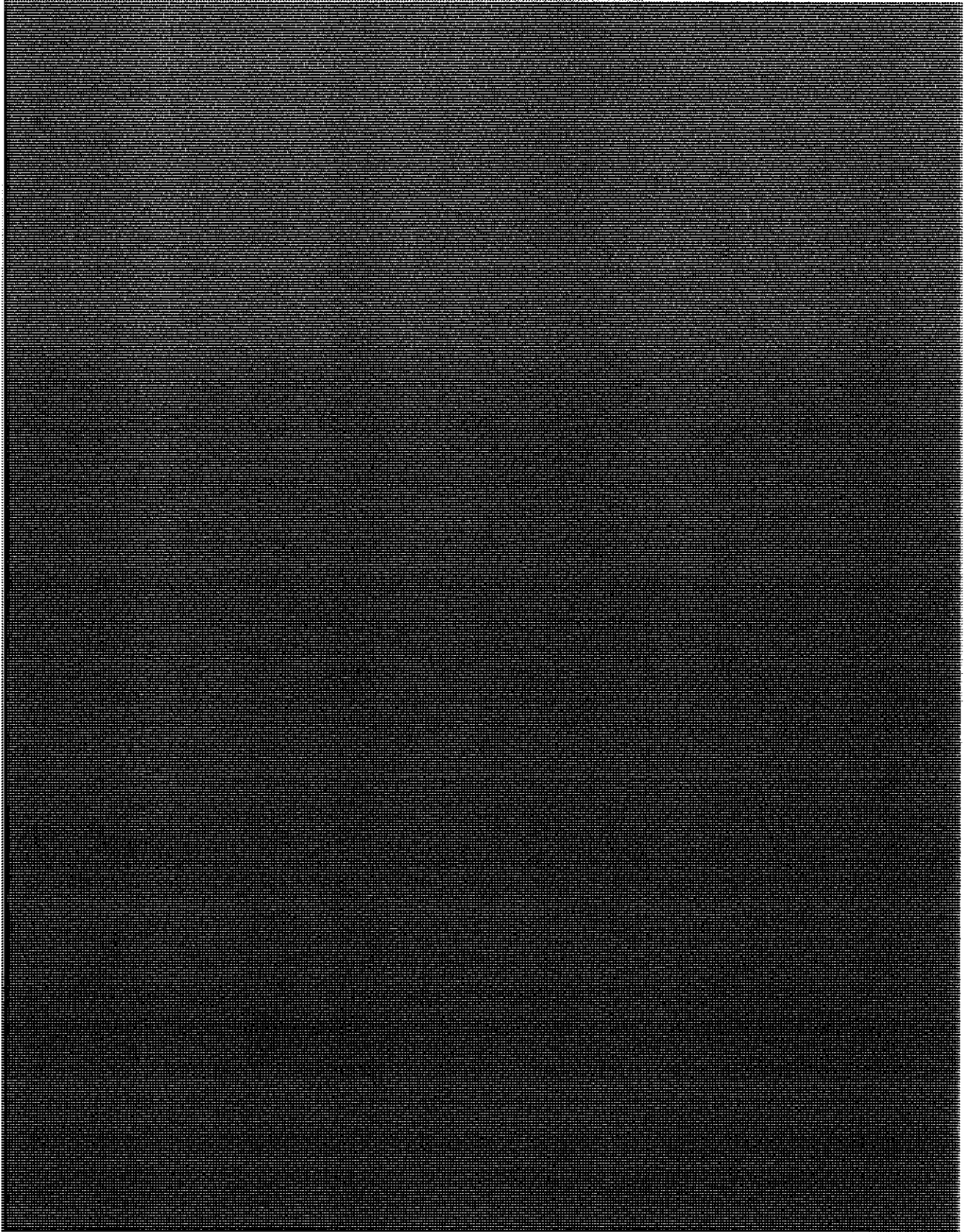


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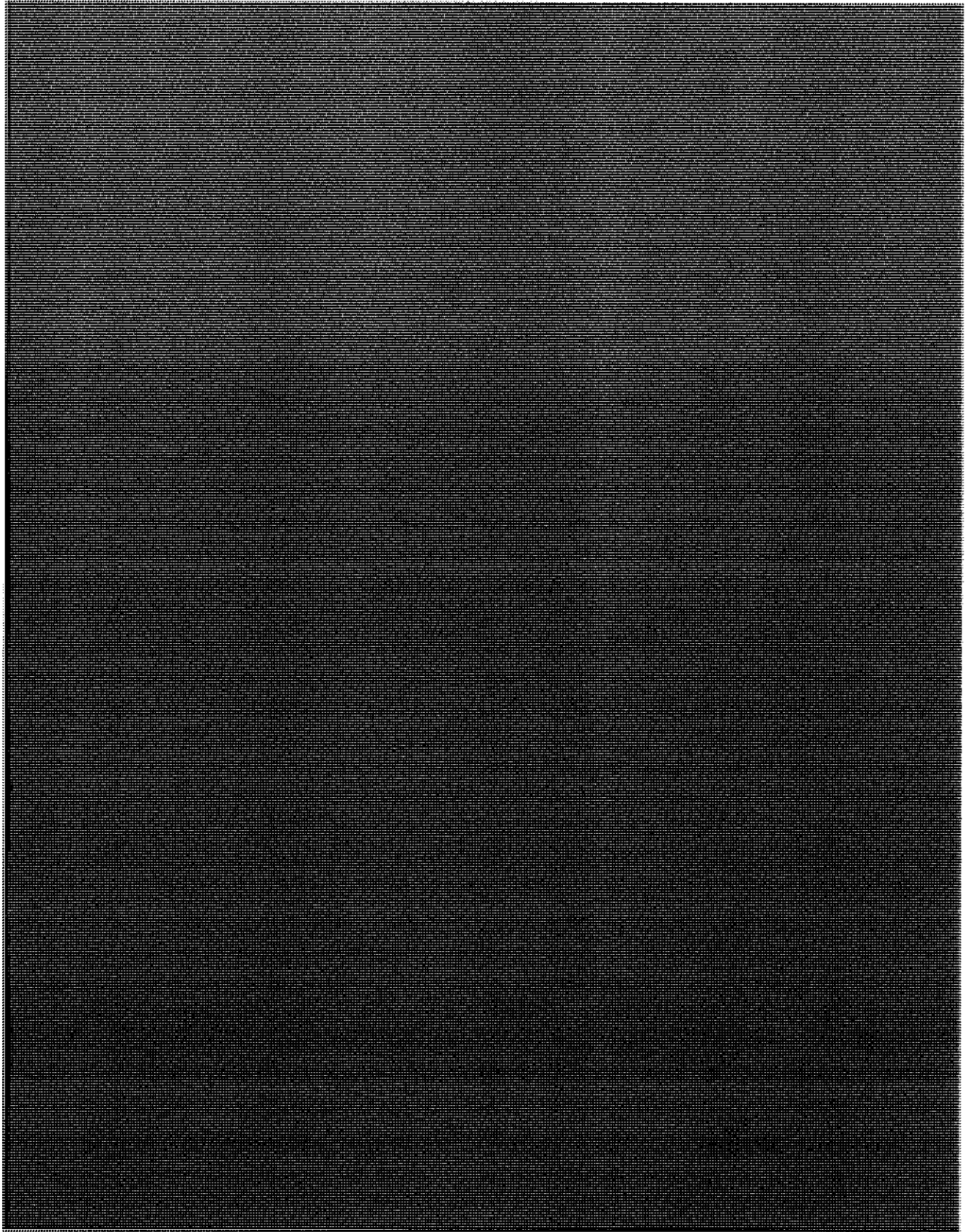
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BPV-17-01-00125422



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BPV-17-01-00125423



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BPV-17-01-00125424

CDRH Cover
Sheet

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CARR EXHIBIT 54, Page 10

BPV-17-01-00125425

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION CDRH PREMARKET REVIEW SUBMISSION COVER SHEET		Form Approval OMB No. 9010-0120 Expiration Date: May 31, 2007. See OMB Statement on page 5.	
Date of Submission 06/03/2005		User Fee Payment ID Number 016997-956733	
		FDA Submission Document Number (if known)	
SECTION A TYPE OF SUBMISSION			
PMA <input type="checkbox"/> Original Submission <input type="checkbox"/> Premarket Report <input type="checkbox"/> Modular Submission <input type="checkbox"/> Amendment <input type="checkbox"/> Report <input type="checkbox"/> Report Amendment <input type="checkbox"/> Licensing Agreement	PMA & HDE Supplement <input type="checkbox"/> Regular (120 day) <input type="checkbox"/> Special <input type="checkbox"/> Panel Track (PMA Only) <input type="checkbox"/> 30-day Supplement <input type="checkbox"/> 30-day Notice <input type="checkbox"/> 135-day Supplement <input type="checkbox"/> Real-time Review <input type="checkbox"/> Amendment to PMA & HDE Supplement <input type="checkbox"/> Other	PDP <input type="checkbox"/> Original PDP <input type="checkbox"/> Notice of Completion <input type="checkbox"/> Amendment to PDP	510(k) <input type="checkbox"/> Original Submission: <input type="checkbox"/> Traditional <input type="checkbox"/> Special <input type="checkbox"/> Abbreviated (Complete section I, Page 5) <input checked="" type="checkbox"/> Additional Information <input type="checkbox"/> Third Party
		Meeting <input type="checkbox"/> Pre-510(K) Meeting <input type="checkbox"/> Pre-IDE Meeting <input type="checkbox"/> Pre-PMA Meeting <input type="checkbox"/> Pre-PDP Meeting <input type="checkbox"/> Day 100 Meeting <input type="checkbox"/> Agreement Meeting <input type="checkbox"/> Determination Meeting <input type="checkbox"/> Other (specify):	
IDE <input type="checkbox"/> Original Submission <input type="checkbox"/> Amendment <input type="checkbox"/> Supplement	Humanitarian Device Exemption (HDE) <input type="checkbox"/> Original Submission <input type="checkbox"/> Amendment <input type="checkbox"/> Supplement <input type="checkbox"/> Report <input type="checkbox"/> Report Amendment	Class II Exemption Petition <input type="checkbox"/> Original Submission <input type="checkbox"/> Additional Information	Evaluation of Automatic Class III Designation (De Novo) <input type="checkbox"/> Original Submission <input type="checkbox"/> Additional Information
		Other Submission <input type="checkbox"/> 513(g) <input type="checkbox"/> Other (describe submission):	
Have you used or cited Standards in your submission? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (If Yes, please complete Section I, Page 5)			
SECTION B SUBMITTER, APPLICANT OR SPONSOR			
Company / Institution Name C.R. Bard, Inc.		Establishment Registration Number (if known) 2020394	
Division Name (if applicable) Bard Peripheral Vascular, Inc		Phone Number (including area code) (480) 303-2720	
Street Address P.O. Box 1740 1625 W. 3 rd Street		FAX Number (including area code) (480) 449-2546	
City Tempe	State / Province AZ	ZIP/Postal Code 85280	Country USA
Contact Name Shari Allen			
Contact Title Director of Regulatory Affairs and Clinical Research		Contact E-mail Address shari.allen@crbard.com	
SECTION C APPLICATION CORRESPONDENT (e.g., consultant, if different from above)			
Company / Institution Name			
Division Name (if applicable)		Phone Number (including area code) ()	
Street Address		FAX Number (including area code) ()	
City	State / Province	ZIP/Postal Code	Country
Contact Name			
Contact Title		Contact E-mail Address	

SECTION D1 REASON FOR APPLICATION - PMA, PDP, OR HDE		
<input type="checkbox"/> Withdrawal <input type="checkbox"/> Additional or Expanded Indications <input type="checkbox"/> Request for Extension <input type="checkbox"/> Post approval Study Protocol <input type="checkbox"/> Request for Applicant Hold <input type="checkbox"/> Request for Removal of Applicant Hold <input type="checkbox"/> Request to Remove or Add Manufacturing Site	<input type="checkbox"/> Change in design, component, or specification: <input type="checkbox"/> Software / Hardware <input type="checkbox"/> Color Additive <input type="checkbox"/> Material <input type="checkbox"/> Specifications <input type="checkbox"/> Other (specify below)	<input type="checkbox"/> Location change: <input type="checkbox"/> Manufacturer <input type="checkbox"/> Sterilizer <input type="checkbox"/> Packager
<input type="checkbox"/> Process change: <input type="checkbox"/> Manufacturing <input type="checkbox"/> Sterilization <input type="checkbox"/> Packaging <input type="checkbox"/> Other (specify below)	<input type="checkbox"/> Labeling change: <input type="checkbox"/> Indications <input type="checkbox"/> Instructions <input type="checkbox"/> Performance <input type="checkbox"/> Shelf Life <input type="checkbox"/> Trade Name <input type="checkbox"/> Other (specify below)	<input type="checkbox"/> Report Submission: <input type="checkbox"/> Annual or Periodic <input type="checkbox"/> Post-approval Study <input type="checkbox"/> Adverse Reaction <input type="checkbox"/> Device Defect <input type="checkbox"/> Amendment
<input type="checkbox"/> Response to FDA correspondence	<input type="checkbox"/> Change in Ownership <input type="checkbox"/> Change in Correspondence <input type="checkbox"/> Change of Applicant Address	
<input type="checkbox"/> Other Reason (specify):		
SECTION D2 REASON FOR APPLICATION - IDE		
<input type="checkbox"/> New Device <input type="checkbox"/> New Indication <input type="checkbox"/> Addition of Institution <input type="checkbox"/> Expansion / Extension of Study <input type="checkbox"/> IRB Certification <input type="checkbox"/> Termination of Study <input type="checkbox"/> Withdrawal of Application <input type="checkbox"/> Unanticipated Adverse Effect <input type="checkbox"/> Notification of Emergency Use <input type="checkbox"/> Compassionate Use Request <input type="checkbox"/> Treatment IDE <input type="checkbox"/> Continued Access	<input type="checkbox"/> Change in: <input type="checkbox"/> Correspondent / Applicant <input type="checkbox"/> Design / Device <input type="checkbox"/> Informed Consent <input type="checkbox"/> Manufacturer <input type="checkbox"/> Manufacturing Process <input type="checkbox"/> Protocol - Feasibility <input type="checkbox"/> Protocol - Other <input type="checkbox"/> Sponsor <input type="checkbox"/> Report submission: <input type="checkbox"/> Current Investigator <input type="checkbox"/> Annual Progress Report <input type="checkbox"/> Site Waiver Report <input type="checkbox"/> Final	<input type="checkbox"/> Repose to FDA Letter Concerning: <input type="checkbox"/> Conditional Approval <input type="checkbox"/> Deemed Approved <input type="checkbox"/> Deficient Final Report <input type="checkbox"/> Deficient Progress Report <input type="checkbox"/> Deficient Investigator Report <input type="checkbox"/> Disapproval <input type="checkbox"/> Request Extension of Time to Respond to FDA <input type="checkbox"/> Request Meeting <input type="checkbox"/> Request Hearing
<input type="checkbox"/> Other Reason (specify):		
SECTION D3 REASON FOR SUBMISSION - 510(k)		
<input type="checkbox"/> New Device	<input type="checkbox"/> Additional or Expanded Indications	<input type="checkbox"/> Change in Technology
<input checked="" type="checkbox"/> Other Reason (specify): Modification to design and limit indications for use.		

SECTION E ADDITIONAL INFORMATION ON 510(K) SUBMISSIONS					
Product codes of devices to which substantial equivalence is claimed					Summary of, or statement concerning, safety and effectiveness information <input type="checkbox"/> 510 (k) summary attached <input checked="" type="checkbox"/> 510 (k) statement
1 DTK	2	3	4	5	
6	7	8	9	10	
Information on devices to which substantial equivalence is claimed (if known)					
	510(k) Number		Trade or Proprietary or Model Name		Manufacturer
1	K022236	1	Recovery Filter System	1	CR Bard
2		2		2	
3		3		3	
4		4		4	
5		5		5	
6		6		6	
SECTION F PRODUCT INFORMATION - APPLICATION TO ALL APPLICATIONS					
Common or usual name or classification Vena Cava Filter					
	Trade or Proprietary or Model Name for This Device				Model Number
1	Recovery Filter System				1 RF-210F
2					2
3					3
4					4
5					5
FDA document numbers of all prior related submissions (regardless of outcome)					
1 K022236	2 K031328	3	4	5	6
7	8	9	10	11	12
Data Included in Submission <input checked="" type="checkbox"/> Laboratory Testing <input checked="" type="checkbox"/> Animal Trials <input type="checkbox"/> Human Trials					
SECTION G PRODUCT CLASSIFICATION - APPLICATION TO ALL APPLICATIONS					
Product Code DTK	C.F.R. Section (if applicable) 21CFR870.3375		Device Class <input type="checkbox"/> Class I <input checked="" type="checkbox"/> Class II <input type="checkbox"/> Class III <input type="checkbox"/> Unclassified		
Classification Panel Cardiovascular					
Indications (from labeling) The Recovery Filter System is indicated for use in the prevention of recurrent pulmonary embolism via permanent placement in the vena cava in the following situations:					
<ul style="list-style-type: none"> Pulmonary thromboembolism when anticoagulants are contraindicated. Failure of anticoagulant therapy for thromboembolic disease. Emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced. Chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated. 					
Note: Submission of this information does not affect the need to submit a 2891 or 2891a Device Establishment Registration form				FDA Document Number (if known)	

FORM FDA 3514 (6/04)

PAGE 3 of 5 PAGES

CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER

CARR EXHIBIT 54, Page 13

BPV-17-01-00125428

SECTION H MANUFACTURING / PACKAGING / STERILIZATION SITES RELATING TO A SUBMISSION					
<input checked="" type="checkbox"/> Original <input type="checkbox"/> Add <input type="checkbox"/> Delete	FDA Establishment Registration Number 1313046		<input checked="" type="checkbox"/> Manufacturer <input type="checkbox"/> Contract Manufacturer	<input type="checkbox"/> Contract Sterilizer <input type="checkbox"/> Repackager / Relabeler	
Company / Institution Name C.R. Bard, Inc			Establishment Registration Number 2020394		
Division Name (if applicable) Bard Peripheral Vascular, Inc			Phone Number (including area code) (480) 303-2720		
Street Address P.O. Box 1740 1625 W. 3 rd Street			FAX Number (including area code) (480) 449-2546		
City Tempe			State / Province AZ	ZIP/Postal Code 85281	Country USA
Contact Name Shari Allen		Contact Title Director of Regulatory Affairs and Clinical Research		Contact E-mail Address shari.allen@crbard.com	
<input checked="" type="checkbox"/> Original <input type="checkbox"/> Add <input type="checkbox"/> Delete	FDA Establishment Registration Number 2212754		<input type="checkbox"/> Manufacturer <input type="checkbox"/> Contract Manufacturer	<input checked="" type="checkbox"/> Contract Sterilizer <input type="checkbox"/> Repackager / Relabeler	
Company / Institution Name CR Bard, Inc.			Establishment Registration Number 2212754		
Division Name (if applicable) Bard Medical, Regional Sterilization			Phone Number (including area code) (770) 784-6130		
Street Address 8195 Industrial Blvd			FAX Number (including area code) (770) 784-6416		
City Covington			State / Province Georgia	ZIP/Postal Code 30014	Country USA
Contact Name Rachel Lovett		Contact Title Quality Assurance		Contact E-mail Address rachel.lovett@crbard.com	
<input type="checkbox"/> Original <input type="checkbox"/> Add <input type="checkbox"/> Delete	FDA Establishment Registration Number		<input type="checkbox"/> Manufacturer <input type="checkbox"/> Contract Manufacturer	<input type="checkbox"/> Contract Sterilizer <input type="checkbox"/> Repackager / Relabeler	
Company / Institution Name			Establishment Registration Number		
Division Name (if applicable)			Phone Number (including area code) ()		
Street Address			FAX Number (including area code) ()		
City			State / Province	ZIP/Postal Code	Country
Contact Name		Contact Title		Contact E-mail Address	

SECTION I		UTILIZATION OF STANDARDS			
Note: Complete this section if your application or submission cites standards or includes a "Declaration of Conformity to a Recognized Standard" statement.					
1	Standards No.	Standards Organization	Standards Title	Version	Date
	10993-7:1995	ISO	Biological Evaluation of Medical Devices Part 7	1995	08/14/1998
2	Standards No.	Standards Organization	Standards Title	Version	Date
	11135:1994	ANSI/AAMI/ISO	Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization	1994	05/31/2002
3	Standards No.	Standards Organization	Standards Title	Version	Date
	ST72:2002	ANSI/AAMI	Bacterial Endotoxins – Test Methodologies	2002	09/01/2004
4	Standards No.	Standards Organization	Standards Title	Version	Date
	14971:2000	ISO	Medical Device – Application of Risk Management to Medical Devices	2000	12/15/2000
5	Standards No.	Standards Organization	Standards Title	Version	Date
	1441:1998	BS EN	Medical Device – Risk Analysis	1998	03/15/1998
6	Standards No.	Standards Organization	Standards Title	Version	Date
7	Standards No.	Standards Organization	Standards Title	Version	Date
Please include any additional standards to be cited on a separate page.					
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BPV-17-01-00125431



Recovery® Filter System

Traditional 510(k) Submission

3 June 2005

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**Bard Peripheral Vascular, Inc
C.R. Bard
1625 West Third Street
P.O. Box 1740
Tempe, AZ 85280-1740**

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Section 1

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Recovery[®] Filter System

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I. Screening Checklist

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Recovery® Filter System

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Screening Checklist for All Premarket Notification 510(k) Submissions

Section 1: Required Elements for All Types of 510(k) Submissions:

Required Element	Location in 510(k)
Cover letter, containing the elements listed on page 3-2 of the Premarket Notification [510] Manual.	See Cover Letter
Table of Contents.	Page 2
Truthful and Accuracy Statement.	Page 10 and Appendix 3
Device's Trade Name, Device's Classification Name and Establishment Registration Number.	Page 8
Device Classification Regulation Number and Regulatory Status (Class I, Class II, Class III or Unclassified)	Page 8
Proposed Labeling including the material listed on page 3-4 of the Premarket Notification [510] Manual.	Page 9 and Appendix 1
Statement of Indications for Use that is on a separate page in the premarket submission.	Page 9 and Appendix 2
Substantial Equivalence Comparison including comparisons of the new device with the predicate in areas that are listed on page 3-4 of the Premarket Notification [510] Manual.	Page 16
510(k) Summary	Page 10 and Appendix 4
Description of the device (or modification of the device) including diagrams, engineering drawings, photographs or service manuals.	Page 11 and Appendix 5
Identification of legally marketed predicate device.*	Section III
Compliance with performance standards.* [Section 514 of the Act and 21 CFR 807.87 (d).]	NA
Class III Certification and Summary.**	NA
Financial Certification or Disclosure Statement for 510(k) notifications with a clinical study.* [See 21 CFR 807.87 (ii)]	NA
510(k) Kit Certification***	NA

* - May not be applicable for Special 510(k)s.

** - Required for Class III devices, only.

***- See pages 3-12 and 3-13 in the Premarket Notification [510] Manual and the Convenience Kits Interim Regulatory Guidance.

Traditional 510(k)
Recovery® Filter System

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Section 2: Additional Required Elements for a TRADITIONAL 510(k) Submission:

Required Element	Location in 510(k)
Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation	Page 32 and Appendix 8
Sterilization and expiration dating information:	Page 31
Sterilization process:	
Validation method of sterilization process	Page 31
SAL	Page 31
Packaging	Page 31
Specify Pyrogen Free	Page 31
ETO residues	Page 31
Radiation Dose	N/A
Traditional Method or Non-Traditional Method	Traditional
Software Documentation	N/A

Section II

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Traditional 510(k)
Recovery[®] Filter System

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II. Required Information

**Traditional 510(k)
Recovery[®] Filter System**

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A. Subject Device Name

Device Trade Name	Common Name
Recovery [®] Filter System	Vena Cava Filter

B. List of Item Numbers for Subject Device

Catalog Number	Description
RF-310F	Recovery Filter System -- Femoral Delivery Kit

For inventory management purposes, a new item number was assigned to the subject device.

C. Classification of the Device/Classification Panel

The vena cava filters have been classified as Class II (with special controls) with product code DTK. The Classification Panel is Cardiovascular.

The special controls for this device are the following:

- FDA's "Guidance for Cardiovascular Intravascular Filter 510(k) Submissions", issued on November 26, 1999.
- BS EN 12006-3:1999 entitled, "Non-Active Surgical Implants - Particular Requirements for Cardiac and Vascular Implants - Part 3: Endovascular Devices".

D. Addresses and Facility Registration Numbers

The address and registration number for the manufacturer and the sterilization site is noted below:

Manufacturer:

Bard Peripheral Vascular, Inc
1625 W. Third Street
PO Box 1740
Tempe, AZ 85280-1740

Establishment Registration Number: 2020394

**Traditional 510(k)
Recovery[®] Filter System**

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Sterilization Facility:

CR Bard, Inc.
Bard Medical
Regional Sterilization
8195 Industrial Blvd
Covington, GA 30014

Establishment Registration Number: 1018233

E. Performance Standards

No performance standards have been developed under Section 514 of the FD&C Act for cardiovascular intravascular filters.

F. Labeling and Intended Use

Draft Labeling

Draft Instructions for Use (IFU) are provided in Appendix 1.

Indications for Use

The Recovery Filter System is indicated for use in the prevention of recurrent pulmonary embolism via permanent placement in the vena cava in the following situations:

- Pulmonary thromboembolism when anticoagulants are contraindicated.
- Failure of anticoagulant therapy for thromboembolic disease.
- Emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced.
- Chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated.

The subject device has the same intended use as the predicate device: the Recovery Filter System (RF-048F) received FDA clearance to market via K022236 on 11/27/02.

The Indications for Use Statement for the subject device is provided in Appendix 2.

Traditional 510(k)
Recovery[®] Filter System

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G. Truthful and Accuracy Statement

The Truthful and Accuracy Statement is provided in Appendix 3.

H. Summary of Safety and Effectiveness

The Summary of Safety and Effectiveness is provided in Appendix 4.

Section III

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III. Device Description and Comparisons

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A. Description of Predicate Device

The Recovery Filter System (RF-048F) received FDA clearance as a permanent filter under K022236 on 11/27/02. The Recovery Filter System consists of the Recovery Filter loaded into a femoral delivery system. The Recovery Filter is intended to be used in IVCs with diameters of ≤ 28 mm. The following is a description of the device cleared in K022236:

The Recovery Filter consists of twelve, shape-memory nitinol wires attached by a ball weld to a central nitinol sleeve. This sleeve provides the attachment point for percutaneous filter removal from the inferior vena cava (IVC). Six wires form an upper "open-dome" and six wires form a lower leg cone. The dome arms and cone legs are offset by 30° to produce a two-level system to mechanically filter pulmonary emboli. (b)(4)

(b)(4)

(b)(4) The cone legs provide the first level of mechanical filtration for pulmonary emboli. There are hooks at the end of each leg that become secured to the IVC wall. The hooks are designed to provide migration resistance when the filter is occluded with emboli.

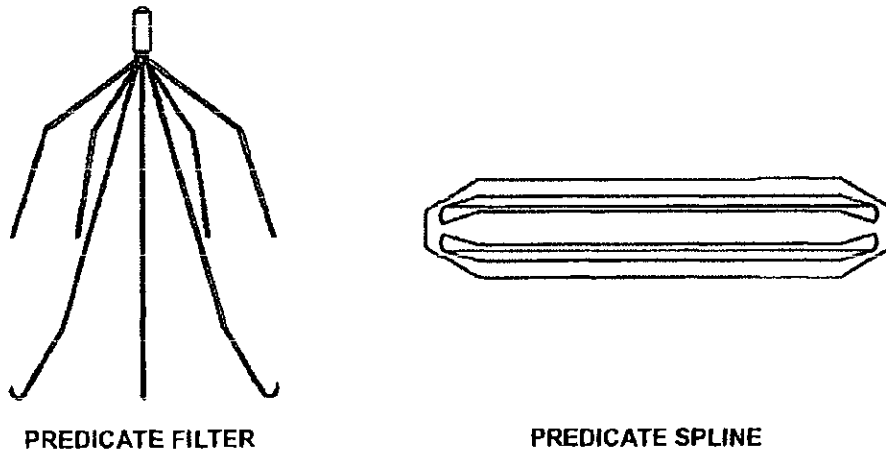
The filter is pre-loaded in a "dome-first" manner into a storage tube in the delivery system. This storage tube is connected to a Y-adaptor and pusher wire which advances the filter through the introducer sheath. The filter returns to its original shape, a dome configuration above six legs, when warmed to body temperature in the IVC.

The femoral delivery system is designed to advance through a 48 cm, 7 French I.D. introducer catheter using a flexible, nitinol pusher wire. A pad at the end of the wire is designed to push on the filter apex and a grooved segment (spline) is designed to hold and properly orient the filter legs. These components secure the filter to the pusher wire as it advances the filter, tip first, to the distal end of the catheter, positioned 1 cm below the lowest renal vein. When the tip of the filter approaches the tip of the introducer catheter, it will be positioned between the radiopaque markers on the introducer catheter. The introducer catheter and delivery assembly are then pulled back onto the pusher wire handle to unsheath and release the filter and allow it to recover to its

predetermined shape. The delivery system allows the Recovery Filter to be deployed with the filter tip centered and is intended to prevent the legs from crossing.

An illustration of the Recovery Filter and spline are provided in Figure 1 with key components identified. Engineering drawings are provided in Appendix 5.

Figure 1. Predicate Device



B. Subject Device Description

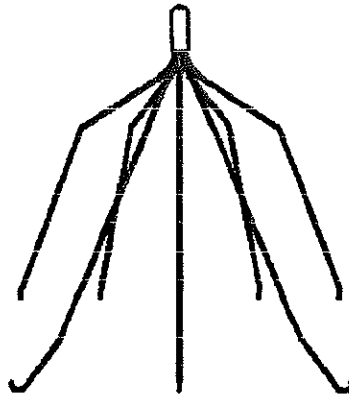
The subject device description is identical to the predicate Recovery Filter System description. The modifications made to the Recovery Filter and delivery system are primarily dimensional. No material changes or additional components have been incorporated.

The dimensional modifications to the Recovery Filter System were made as a part of the total product life cycle (TPLC) management process with the intent of increasing filter migration resistance and reduction of filter arm fractures. In addition, the delivery system spline has been modified to accommodate the dimensional modifications to the hooks of the filter.

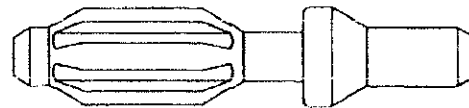
The purpose of this Traditional 510(k) is to introduce a modified Recovery Filter System (Item RF-310F). Illustrations of the modified filter and delivery system spline are

provided in Figure 2 with key components identified. Engineering drawings are provided in Appendix 5.

Figure 2. Subject Device



SUBJECT DEVICE FILTER



SUBJECT DEVICE SPLINE

C. Comparison Summary

The differences between the predicate and the subject device are the following:

- (b)(4)
-
-
-
-
-

Figure 3. illustrates these differences between the predicate and the subject device.

Figure 3. Illustration of the Differences Between the Predicate and the Subject

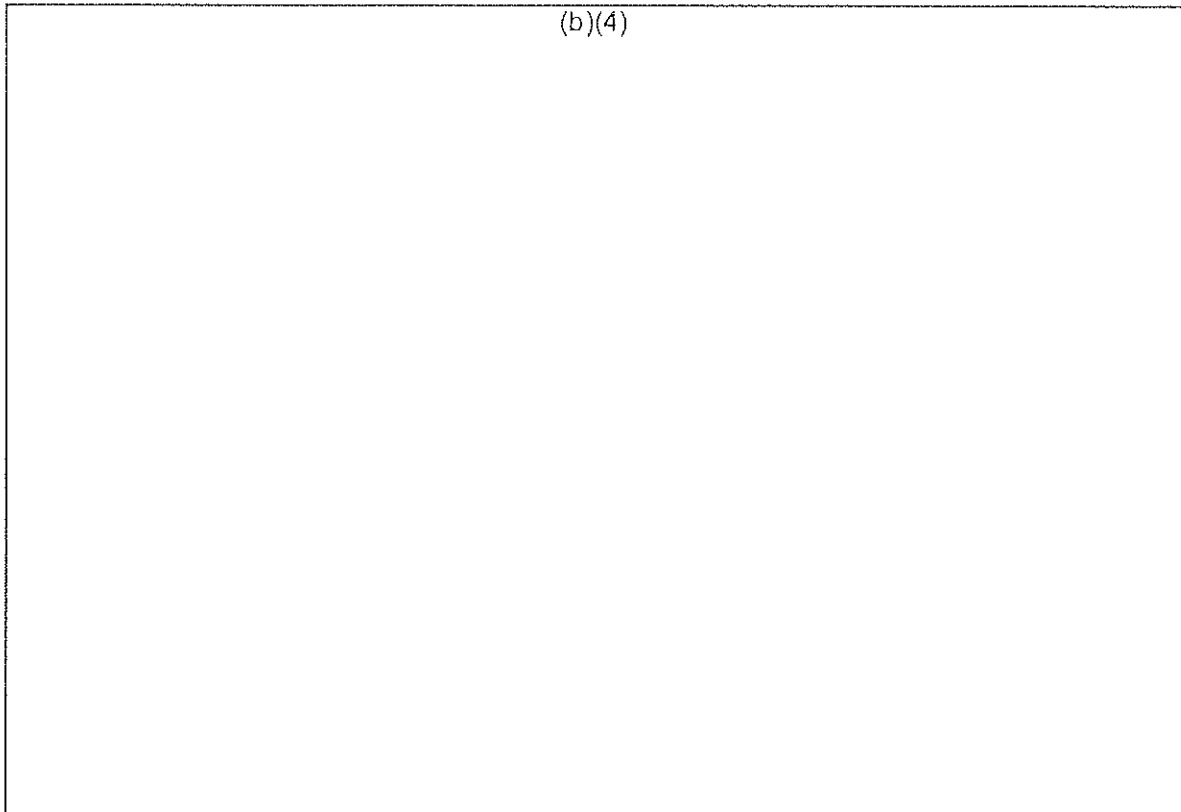


Table 2 describes the design characteristics that were not affected by the modifications made to the predicate device.

Table 2. Design Characteristics Not Affected by Design Changes

Characteristic	Rationale
Clot Capturing Ability	The subject device filter arm and leg diameters are the same as the predicate device filter when constrained in an IVC lumen up to 28 mm in diameter as defined by the IFU making the luminal cross section of the subject device filter identical to the predicate device filter. Therefore, the filter clot capturing ability is not affected.
Filter Height	The subject device is annealed using the same jig as the predicate device; therefore, the height of the subject filter is the same as the predicate device when constrained in an IVC lumen up to 28 mm in diameter as defined by the IFU. The difference in the nominal height between the subject and predicate filters is due to the difference in the leg span in the unconstrained state. The relationship between the leg span and the height can be described as follows: the wider the leg span (e.g. due to a larger diameter IVC), the shorter the filter height.
Filter Deployment	This characteristic relates to the clinical technique of filter deployment. The method of delivery has not changed. Therefore, further evaluation of this characteristic is not required.
Delivery of Filter Through Femoral Vein	The procedural instructions have not changed. Therefore, further evaluation of this characteristic is not required.
Biocompatibility	Biocompatibility testing was performed on the predicate device. All materials used in the subject device are identical to the predicate device. Therefore, the biological testing reports from the predicate device remain applicable and no further biological testing is required.
Shelf-Life/Stability	The predicate device has been proven to be stable after 3-year accelerated aging. The materials for the subject device are identical and the stresses are equivalent to or lower than those of the predicate device, as determined by Finite Element Analysis. Therefore, the subject device does not require further stability testing and will adopt the 3-year shelf life of the predicate device.
MRI Compatibility	All materials used in the subject device are identical to the predicate device. The MRI testing report from the predicate device successfully met the MRI compatibility test requirements. Therefore, the subject device will not require further MRI compatibility testing.

E. Summary of Substantial Equivalence

The subject device has the following similarities to the predicate device that received clearance to market via K022236 on 11/27/02:

- Same intended use and indications for use;
- Same filter and delivery system materials;
- Same operating principle;
- Same fundamental scientific technology;
- Same packaging configuration and materials;
- Same sterility assurance level and method of sterilization.

Based upon the similarities to the predicate device and the design verification and validation data (bench and animal) provided in Section IV, the modified Recovery Filter System is substantially equivalent to the predicate Recovery Filter System (K022236).

Section IV

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Recovery[®] Filter System

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IV. Design Control Activities

A. Summary of Design Control Activities**1. Risk Analysis**

A Risk Assessment and a Design Failure Modes and Effects Analysis (DFMEA) of the subject device were conducted in accordance with internal procedures based on ISO 14971:2000, Medical Devices – Application of risk management to medical devices and BS EN 1441: 1998, Medical Devices-Risk Analysis to assure that risks posed by the subject design are acceptable. The analysis did not identify any new types of safety or effectiveness questions for the modified device. The analysis identified the verification and validation activities required to assure that any risks associated with the modified design are acceptable.

The outcome of the overall Risk Management process demonstrated that the Recovery Filter System presents an acceptable level of risk for its intended use. Based upon the risk analysis performed regarding the modifications described Table 1, the verification and validation activities described in Table 3 demonstrate that the design output of the subject device met the device input and user needs requirements.

As identified in the DFMEA, design verification tests were designed and performed to demonstrate that the modified device met performance specifications to assure that there were no increased risks associated with the modification compared to the predicate design. Table 3 describes each bench test performed, the acceptance criteria, results for each test, and required sample sizes.

Design verification testing was performed with consideration to the FDA Special Controls guidance document, "Guidance for Cardiovascular Intravascular Filter 510(k) Submissions", issued on November 26, 1999 and BS EN 12006-3:1999 entitled, "Non-Active Surgical Implants - Particular Requirements for Cardiac and Vascular Implants - Part 3: Endovascular Devices".

2. Summary of Design Verification/Validation Activities

The only modifications (see Comparison Summary section) to the Recovery Filter System are the dimensional changes to the filter arms and hooks as well as the delivery system spline. All other aspects of the subject device filter and delivery system have been previously verified and validated with the predicate device.

Verification and validation of the design changes was performed according to the recommendations of the FDA guidance document, Design Control Guidance for Medical Device Manufacturers, dated March 11, 1997. All verification and validation testing was performed under defined operating conditions on initial, sterilized (b)(4) units or their equivalents.

The subject device filter met all the predetermined design verification and validation requirements as described in Table 3. See Table 3 for a more detailed, tabular summary and Appendix 6 for a copy of the design verification and validation test protocol and test report. *[Editorial Note: The design verification and validation testing was performed to evaluate the retrievability of the Recovery Filter; however, Bard Peripheral Vascular, Inc. is not requesting clearance of this indication at this time, and the testing is being reported for consistency purposes only.]*

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Traditional 510(k)
Recovery® Filter System

Table 3. Design Verification and Validation for the Subject Device

(b)(4)	
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Traditional 510(k)
Recovery[®] Filter System

Table 3. Design Verification and Validation for the Subject Device

(b)(4)

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Recovery® Filter System

Table 3. Design Verification and Validation for the Subject Device

(b)(4)

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Table 3. Design Verification and Validation for the Subject Device

(b)(4)

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Table 3. Design Verification and Validation for the Subject Device

(b)(4)	
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Recovery® Filter System

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Table 3. Design Verification and Validation for the Subject Device

(b)(4)	
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3.1 Model Description for Acute and Chronic Studies

Consequently, the use of larger animal models, such as sheep, has become more common for this evaluation. The large vessels of the sheep are similar in size to human vessels which provide expected clinical conditions for the subject device. If a device can be safely deployed in the vena cava of sheep, there is reasonable assurance that the device will perform safely and effectively within the vena cava of humans.

3.2.1 Objectives

.....

(b)(4)

1001

(b)(4)

BAIRD

Traditional 510(k)
Recovery® Filter with Femoral Delivery

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(b)(4)

3.2.3 Conclusion

(b)(4)

3.3 Chronic In-Vivo Study - Filter

3.3.1 Objectives

The objective of this study was to evaluate the following:

- (b)(4)
-
-

[Editorial Note: The design verification and validation testing was performed to evaluate the retrievability of the Recovery Filter; however, Bard Peripheral Vascular, Inc. is not requesting clearance of this indication at this time, and the testing is being reported for consistency purposes only.]

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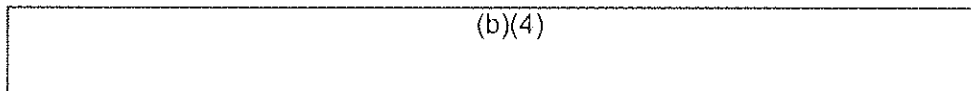
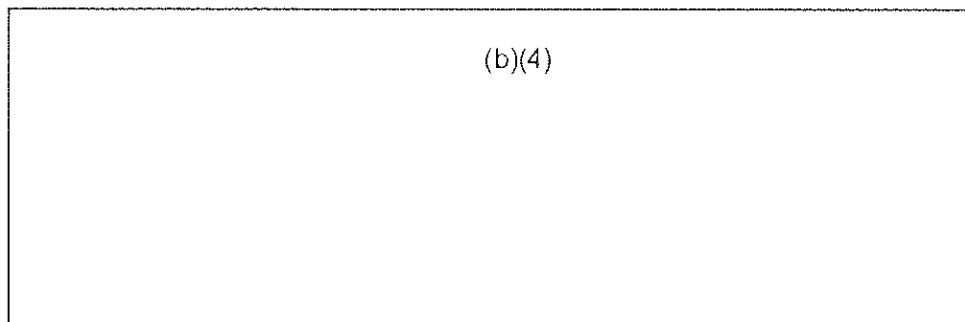
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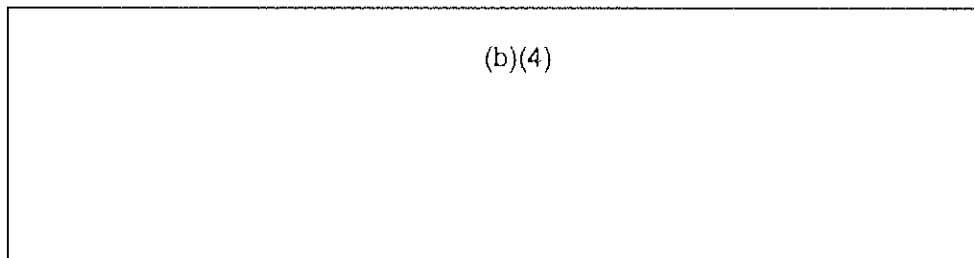
BPV-17-01-00125464

The following table describes the design of this study:

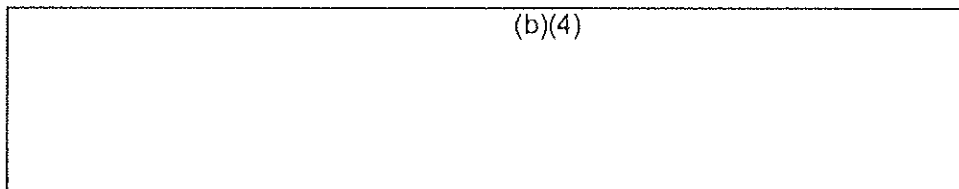
Figure 2. Subject Device Animal Study Design



3.3.2 Results



3.3.3 Conclusion



**Traditional 510(k)
Recovery® Filter with Femoral Delivery**

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B. Packaging

The packaging configuration and materials for the predicate (K022236) and subject devices are identical.

C. Sterilization

(b)(4)

D. Shelf-Life

(b)(4)

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Recovery[®] Filter with Femoral Delivery**

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(b)(4)

E. Biocompatibility Testing

All materials and manufacturing processes for the subject device are identical to the predicate device (K022236). A material certification for the components and device is provided in Appendix 8.

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Appendix 1

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Appendix 1 - Labeling

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Draft Package Labeling

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RECOVERY[®]

Filter System

FEMORAL INTRODUCER CATHETER

REF: RF-210F

Contents: NO. A One (1) F. Introducer Catheter
40cm Long with Dilator
(Recommended Guidewire 0.038")



LOT: XXXXXXX

⚠ Attention: See Information For Use

② Single Use. Do Not Reuse.

③ Do Not Reinsertion.

④ Remove Single Use Catheter in One Piece.

⑤ Dispose of this device in accordance with applicable federal, state and local regulations.

Caution: Federal (USA) law restricts this device to sale by or on the order of a Physician.


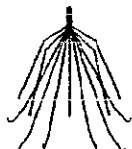
BAIRD

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Recovery® Filter System

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KIT B POUCH LABEL

															
FEMORAL		REF: RF-210F													
1 Contents: Kit B: One (1) Recovery Filter Femoral Delivery System	LOT XXXXXXXX														
		Expiration Date YYY/YY													
Attention, See Information For Use															
2 Single Use. Do Not Reuse		3 Do Not Restrict													
Contents Sterile Unless Package is Damaged or Opened		STERILE EO Sterilized in Ethylen Oxide													
Warning: After use, this product may be a potential biohazard. Handle and dispose of it in accordance with accepted medical practice and applicable laws and regulations.															
NON-PYROGENIC Sterile, non-pyrogenic unless package is damaged or opened.															
MR MRI compatible. MRI-safe and receive interference with nor is affected by the operations of an MRI device.															
Keep Dry		Protect From Heat													
TM Bard and Recovery are registered trademarks of C. R. Bard, Inc. or an affiliate.															
Caution: Federal (USA) law restricts this device to sale by or on the order of a physician. U.S. Patent No. 6,007,558 and 6,258,026. Other patents pending.															
<table border="1"> <tr> <td rowspan="3">BARD</td> <td>Recovery® Filter System</td> </tr> <tr> <td>REF: RF-210F</td> </tr> <tr> <td>LOT XXXXXXXX</td> </tr> <tr> <td rowspan="3">BARD</td> <td>Recovery® Filter System</td> </tr> <tr> <td>REF: RF-210F</td> </tr> <tr> <td>LOT XXXXXXXX</td> </tr> <tr> <td rowspan="3">BARD</td> <td>Recovery® Filter System</td> </tr> <tr> <td>REF: RF-210F</td> </tr> <tr> <td>LOT XXXXXXXX</td> </tr> </table>				BARD	Recovery® Filter System	REF: RF-210F	LOT XXXXXXXX	BARD	Recovery® Filter System	REF: RF-210F	LOT XXXXXXXX	BARD	Recovery® Filter System	REF: RF-210F	LOT XXXXXXXX
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	LOT XXXXXXXX														
BARD		Bard Peripheral Vascular, Inc. P.O. Box 1740 Tempe, AZ 85280-1740 USA TEL: 1-800-494-8515 1-800-321-4254 FAX: 1-800-666-7082 1-800-446-5376 www.bardpv.com													

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OUTER POUCH LABEL

 																
FEMORAL																
Contents: Kit A: One (1) 7 Ft. Introducer Catheter 48cm Long with Dilator Kit B: One (1) Recovery Filter Femoral Delivery System	REF: RF-210F															
LOT XXXXXXXX	Expiration Date YYYY/MM															
Attention, See information For Use																
Single Use. Do Not Reuse	Do Not Reinsert															
Contents Sterile Unless Package is Damaged or Opened	STERILE EO Ethylene Oxide															
Warning: After use, this product may be a potential biohazard. Handle and dispose of in accordance with accepted medical practice and applicable laws and regulations.																
NON-PYROGENIC Sterile, non-pyrogenic unless package is damaged or opened																
MRSA MRSA susceptible MRSA and related infections with MRSA is affected by the presence of an MRSA device																
Keep Dry	Protect From Heat															
TM Bard and Recovery are registered trademarks of C. R. Bard, Inc. or an affiliate.																
Caution: Federal (USA) law restricts this device to sale by or on the order of a physician. U.S. Patent No. 6,007,558 and 6,258,026. Other patents pending.																
<table border="1"> <tr> <td rowspan="4"> BARD </td> <td>Recovery® Filter System</td> </tr> <tr> <td>REF: RF-210F</td> </tr> <tr> <td>LOT XXXXXXXX</td> </tr> <tr> <td> </td> </tr> <tr> <td rowspan="4"> BARD </td> <td>Recovery® Filter System</td> </tr> <tr> <td>REF: RF-210F</td> </tr> <tr> <td>LOT XXXXXXXX</td> </tr> <tr> <td> </td> </tr> <tr> <td rowspan="4"> BARD </td> <td>Recovery® Filter System</td> </tr> <tr> <td>REF: RF-210F</td> </tr> <tr> <td>LOT XXXXXXXX</td> </tr> <tr> <td> </td> </tr> </table>		BARD	Recovery® Filter System	REF: RF-210F	LOT XXXXXXXX		BARD	Recovery® Filter System	REF: RF-210F	LOT XXXXXXXX		BARD	Recovery® Filter System	REF: RF-210F	LOT XXXXXXXX	
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<table border="1"> <tr> <td rowspan="5"> BARD </td> <td>Bard Peripheral Vascular, Inc.</td> </tr> <tr> <td>P.O. Box 1740</td> </tr> <tr> <td>Tampa, AZ 85280-1740</td> </tr> <tr> <td>USA</td> </tr> <tr> <td>TEL: 1-800-894-8515</td> </tr> <tr> <td>1-800-321-4284</td> </tr> <tr> <td>FAX: 1-800-966-1082</td> </tr> <tr> <td>1-800-440-1378</td> </tr> <tr> <td>www.bardpv.com</td> </tr> </table>		BARD	Bard Peripheral Vascular, Inc.	P.O. Box 1740	Tampa, AZ 85280-1740	USA	TEL: 1-800-894-8515	1-800-321-4284	FAX: 1-800-966-1082	1-800-440-1378	www.bardpv.com					
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Bard Peripheral Vascular, Inc

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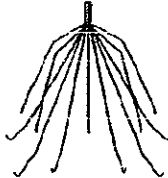









BPV-17-01-00125473

CARR EXHIBIT 54, Page 58

Traditional 510(k)
Recovery® Filter System

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Recovery Filter Unit Box Label

			
FEMORAL		REF: RF-210F	
Contents: Kit A: One (1) 7 Fr. Introducer Catheter 48cm Long with Dilator Kit B: One (1) Recovery Filter Femoral Delivery System			
LOT XXXXXXXX	Expiration Date YYYY/MM		
Attention, See Information For Use			
 Single Use. Do Not Reuse.		 Do Not Reuse.	
 Contents Sterile Unless Package is Damaged or Opened.		STERILE EO Sterilized With Ethylene Oxide	
 Warning: After use, this product may be a potential biohazard. Handle and dispose of in accordance with accepted medical practice and applicable laws and regulations.			
NON-PYROGENIC		Sterile, non-pyrogenic unless package is damaged or opened.	
 MRI compatible: MRI-safe and neither interferes with nor is affected by the operation of an MRI device.			
 Keep Dry		 Protect From Heat	
 Bard and Recovery are registered trademarks of C. R. Bard, Inc. or an affiliate.			
Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.			
U.S. Patent No. 6,007,558 and 6,258,026. Other patents pending.			
		Bard Peripheral Vascular, Inc. P.O. Box 1740 Tempe, AZ 85280-1740 USA TEL: 1-800-894-9515 1-800-321-4254 FAX: 1-800-956-7062 1-800-440-5376 www.bardpv.com	
<div style="border: 1px dashed black; padding: 5px; text-align: center;"> Primary Bar Code <small>Primary Human Readable</small> </div>			
<div style="border: 1px dashed black; padding: 5px; text-align: center;"> Secondary Bar Code <small>Secondary Human Readable</small> </div>			

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BPV-17-01-00125474

CARR EXHIBIT 54, Page 59

Traditional 510(k)
Recovery® Filter System

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Predicate Device 510(k) Concurrence Letter

(Substantially Equivalent with Limitations)

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CARR EXHIBIT 54, Page 60



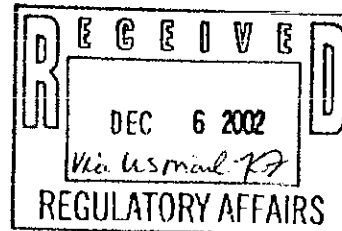
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

NOV 27 2002

Ms. Kay Fuller
Senior Regulatory Affairs Specialist
C. R. Bard, Inc.
1625 West 3rd Street
Tempe, AZ 85281



Re: K022236/S2
Trade/Device Name: Bard® Recovery™ Filter System, Model RF-048F
Regulation Number: 870.3375
Regulation Name: Cardiovascular intravascular filter
Regulatory Class: II
Product Code: DTK
Dated: October 25, 2002
Received: October 29, 2002

Dear Ms Fuller:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act and the limitations described below. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

The Office of Device Evaluation has determined that there is a reasonable likelihood that this device will be used for an intended use not identified in the proposed labeling and that such use could cause harm. Therefore, in accordance with Section 513(i)(1)(E) of the Act, the following limitation must appear in the Precautions section of the device's labeling and in promotional materials:

The safety and effectiveness of the Recovery™ Filter for use as a retrievable or temporary filter have not been established.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

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Page 2 - Ms. Kay Fuller

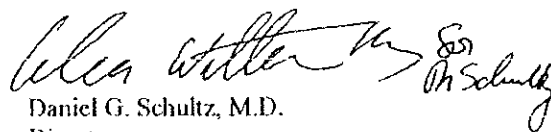
Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and permits your device to proceed to the market. This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification if the limitation statement above is added to your labeling, as described.

Please note that the above labeling limitations are required by Section 513(i)(1)(E) of the Act. Therefore, a new 510(k) is required before these limitations are modified in any way or removed from the device's labeling.

If you desire specific information about the application of other labeling requirements to your device (21 CFR Part 801 and additionally Part 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4586. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address <http://www.fda.gov/cdrh/dsma/dsmamain.html>.

Sincerely yours,



Daniel G. Schultz, M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Page 1 of 1


510(k) Number (if known): K022236

Device Name: Bard® Recovery™ Filter System, Model RF-048F

FDA's Statement of the Indications For Use for device:

The Recovery™ Filter System is indicated for use in the prevention of recurrent pulmonary embolism via permanent placement in the vena cava in the following situations:

- Pulmonary thromboembolism when anticoagulants are contraindicated.
- Failure of anticoagulation therapy for thromboembolic disease.
- Emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced.
- Chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated.


Division of Cardiovascular & Respiratory Devices
510(k) Number K022236

Prescription Use ✓
(Per 21 CFR 801.109)

OR Over-The-Counter Use _____

**Traditional 510(k)
Recovery[®] Filter System**

Page 43

Draft Subject Device Instructions For Use

Bard Peripheral Vascular, Inc

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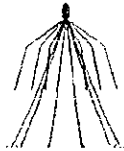
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BPV-17-01-00125479

CARR EXHIBIT 54, Page 64

Recovery® Filter System for use in the Vena Cava



ENGLISH

Information for Use

Caution: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

A. General Information

The Recovery Filter represents a new generation of venous interruption devices designed to prevent pulmonary embolism. The unique design and material of the Recovery Filter provide filtering efficiency and allow permanent placement through a standard 7 French (F) angiographic introducer catheter with minimum entry site difficulties. The placement procedure is quick and simple to perform.

The filter is set designed to advance through a 7 French (F) introducer catheter using a flexible, nitinol pusher wire. A pad at the end of the wire is designed to push on the filter apex and a grooved segment is designed to hold and properly orient the filter legs. These components secure the filter to the pusher wire as it advances the filter, leg first, to the distal end of the catheter, positioned 1 cm below the lowest renal vein. When the tip of the filter approaches the tip of the introducer catheter, it will be positioned between the radiopaque markers on the introducer catheter. The introducer catheter and delivery assembly are then pulled back until the pusher wire handle is unhooked and release the filter and allow it to recover to its predetermined shape. The centering system allows the Recovery Filter to be deployed with the filter by centered and minimizes the potential for legs crossing.

The Recovery Filter is designed to act as a permanent filter.

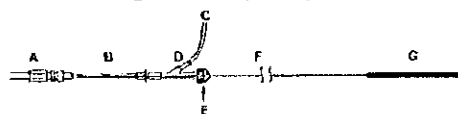
MRI Compatible: The Recovery Filter is MRI safe and neither interferes with nor is affected by the operations of a MRI device.

B. Device Description

The Recovery Filter System consists of the filter and delivery system. The Recovery Filter consists of twelve, shape memory, nitinol legs emanating from a central nitinol sleeve. These twelve legs form two levels of filtration. The legs provide the lower level of filtration and the arms provide the upper level of filtration. The Recovery Filter is intended to be used in the inferior vena cava (IVC) with a diameter less than or equal to 28 mm.

The Recovery Filter Delivery System is illustrated in Figure A. The delivery system consists of a 7 French (F) introducer catheter and dilator, the Recovery Filter, a storage tube with saline infusion port, and a pusher system. The Recovery Filter is packaged pre-loaded within the delivery storage tube.

Figure A. Recovery Filter System



- A. INTRODUCER CATHETER
- B. FILTER STORAGE TUBE
- C. SALINE DRIVE INFUSION SET
- D. STOP PLUG
- E. ADJUSTABLE TOURNIQUET ADAPTER
- F. NITINOL PUSHER WIRE
- G. PUSHER WIRE HANDLE

IMPORTANT: Read instructions carefully before using the Recovery Filter.

C. Indications for Use

The Recovery Filter System is indicated for use in the prevention of recurrent pulmonary embolism via permanent placement in the vena cava in the following situations:

- Pulmonary thromboembolism when anticoagulants are contraindicated
- Failure of anticoagulant therapy for thromboembolic disease
- Emergency treatment following massive pulmonary embolism when anticoagulant benefits of conventional therapy are reduced
- Chronic, recurrent pulmonary embolism when anticoagulant therapy has failed or is contraindicated.

D. Contraindications for Use

CAUTION: If the IVC diameter exceeds 28 mm the filter must not be inserted into the IVC.

The Recovery Filter should not be implanted in:

- Pregnant patients when delivery may endanger the fetus. Risks and benefits should be assessed carefully.
- Patients with an IVC diameter less than 28 mm.
- Patients with risk of septic embolism.

E. Warnings

Recovery Filter Implantation

- The Recovery Filter is pre-loaded into the storage tube and is intended for single use only. Do not deploy the filter prior to proper positioning in the IVC, as the Recovery Filter cannot be safely retrieved into the storage tube.
- Do not deploy the filter unless IVC has been properly measured. (Refer to Precaution #4.)
- Delivery of the Recovery Filter through the introducer catheter in advance only. Retraction of the pusher wire during delivery could result in dislodgment of the filter, crossing of filter legs in apex, and could prevent the filter from further advancement within the introducer catheter.

- The Recovery Filter System is designed for femoral approaches only. Never use the Recovery Filter and Delivery System for superior approaches (jugular, subclavian or axillofemoral veins), as this will result in improper Recovery Filter orientation within the IVC.
- If large thrombus is demonstrated at the initial delivery site, do not attempt to deliver the filter through it as migration of the clot and/or filter may occur. Attempt filter delivery through an alternate site. A small thrombus may be bypassed by the guidewire and introducer catheter.
- Never advance the guidewire or introducer catheter inferiorly or deploy the filter without fluoroscopic guidance.
- Filter fracture is a known complication of vena cava filters. There have been reports of embolization of vena cava filter fragments resulting in retrieval of the fragment using endovascular and/or surgical techniques. Most cases of filter fracture, however, have been reported without any adverse clinical sequelae.
- Movement or migration of the filter is a known complication of vena cava filters. This may be caused by placement in IVCs with diameters exceeding the appropriate labeled dimensions specified in the IFU. Migration of filters to the heart or lungs have been reported in association with improper deployment, deployment into clot and/or dislodgment due to large clot burdens.

See Potential Complications section for further information regarding other known filter complications.

F. Precautions

Recovery Filter Implantation

1. The filter should be placed in the supine position in pregnant women and in women of childbearing age.
2. Anatomical variations may complicate filter insertion and deployment. Careful attention to these instructions for use can shorten insertion time and reduce the likelihood of difficulties.
3. Position the filter to 1 cm below the lowest renal vein. Venacavography must always be performed to confirm proper implant site. Radiographs without contrast, which do not clearly show the wall of the IVC, may be misleading.
4. When measuring caval dimensions, consider an angiographic catheter or intra-venous ultrasound (IVUS) if there is any question about caval morphology.
5. Spinal deformations: It is important to exercise care when contemplating implantation in patients with significant kyphosis or other spinal deformations because the IVC may follow the general course of such anatomic deformations.
6. In patients with continued risk of chronic, recurrent pulmonary embolism, patients should be returned to anti-thrombotic therapy as soon as it is deemed safe.
7. If resistance is encountered during femoral insertion procedure, withdraw the guidewire and check with patency flushes regularly with a small hypodermic syringe. If a large thrombus is demonstrated, remove the response needle and use the vein on the opposite side. A small thrombus may be bypassed by the guidewire and introducer.
8. The introducer catheter has radiopaque markers to assist in visualization and predeployment filter positioning. The radiopaque markers on the introducer catheter provide a target location between which the filter should be positioned just prior to unsheathing and deployment.
9. The introducer catheter hub has a special internal design. Care should be taken to make connections firmly, but without excessive force that may cause breakage of the hub.
10. It is very important to maintain introducer catheter patency with the saline flush so that the grooved segment that holds and properly orients the filter legs does not become covered by clot. This will interfere with filter deployment.
11. Do not deliver the filter by pushing it beyond the end of the introducer catheter. To achieve proper placement, unsheath the stationary filter by withdrawing the introducer catheter.

The safety and effectiveness of the Recovery Filter for use as a retrievable or temporary filter have not been established.

G. Potential Complications

Procedures requiring permanent interventional techniques should not be attempted by physicians unfamiliar with the possible complications. Complications may occur at any time during or after the procedure.

Possible complications include, but are not limited to, the following:

- Movement or migration of the filter is a known complication of vena cava filters. This may be caused by placement in IVCs with diameters exceeding the appropriate labeled dimensions specified in the IFU. Migration of filters to the heart or lungs have also been reported in association with improper deployment, deployment into clot and/or dislodgment due to large clot burdens.
- Filter fracture is a known complication of vena cava filters. There have been reports of embolization of vena cava filter fragments resulting in retrieval of the fragment using endovascular and/or surgical techniques. Most cases of filter fracture, however, have been reported without any adverse clinical sequelae.
- Perforation or other acute or chronic damage of the IVC wall.
- Acute or recurrent pulmonary embolism. This has been reported despite filter usage. It is not known if thrombus passed through the filter, or originated from superior or collateral vessels.
- Caval thrombotic occlusion.
- Extravasation of contrast material at time of venacavogram.
- Air embolism.
- Hematoma or nerve injury at the puncture site or subsequent retrograde air.
- Hemorrhage.
- Restriction of blood flow.
- Occlusion of small vessels.
- Deep vein thrombosis.
- Infection.
- Intimal tear.
- Stenosis at implant site.

All of these above complications have been associated with serious adverse events such as medical intervention and/or death. There have been reports of complications including death, associated with the use of the Recovery Filter System in morbidly obese patients. The risk/benefit ratio of any of these complications should be weighed against the inherent risk/benefit ratio for a patient who is at risk of pulmonary embolism without intervention.

H. Equipment Required

The following equipment is required for use:
One Recovery Filter and Delivery System that contains:

- One 48 cm, 7 French IVC introducer catheter and dilator set
- One storage tube with pre-loaded Recovery Filter and pusher delivery system
- 0.031" 3 mm J-tipped guidewire, 115 cm long or longer
- 18 gauge entry needle
- Saline
- Sterile extension tube for saline drip or syringe for saline infusion
- All basic materials for venipuncture: scalpel, #11 blade, local anesthesia, drape, etc.

1. Instructions for Use

Insertion of the 7 French Introducer Catheter and Preliminary Venography

1. Select a suitable femoral venous access route, on either the right or left side, depending upon the patient's size or anatomy, operator's preference or location of venous thrombosis.
2. Prep, drape and anesthetize the skin puncture site in standard fashion.
3. Stereotactically insert the filter package. Open the 7 French Introducer Catheter package.
4. Nick the skin with a #11 blade and perform venipuncture with an 18 gauge entry needle.
5. Insert the J-tipped guidewire and gently advance into the distal vena cava or iliac vein.

NOTE: If resistance is encountered during a femoral insertion procedure, withdraw the guidewire and check vein patency fluoroscopically with a small injection of contrast medium. If a large thrombus is demonstrated, remove the venipuncture needle and try the vein on the opposite side. A small thrombus may be bypassed by the guidewire and introducer.

6. Remove the venipuncture needle over the J-tipped guidewire. Advance the 7 French Introducer Catheter together with its tapered dilator over the guidewire and into the distal vena cava or iliac vein.

NOTE: The introducer catheter has radiopaque markers to assist in visualization and predelivery filter positioning. The radiopaque markers on the introducer catheter provide a "target" location between which the filter should be positioned just prior to unsheathing and deployment.

7. Remove the guidewire and dilator, leaving the introducer catheter with its tip in the distal vena cava or iliac vein. Flush intermittently by hand or attach to the introducer catheter a constant saline drip infusion to maintain introducer catheter patency.

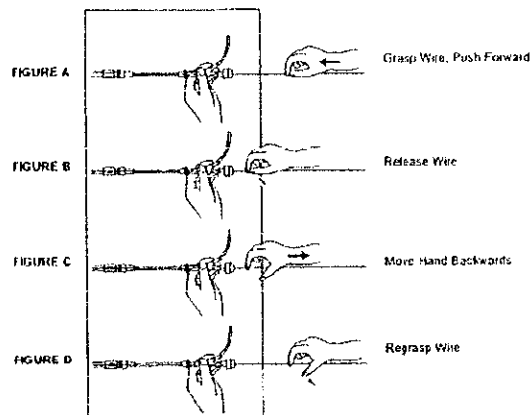
NOTE: The introducer catheter has a special internal design. Care should be taken to make connections firmly, but without excessive force that may cause leakage in the hub.

- A. Perform a standard inferior venaogram (typically 30 ml of contrast medium at 15 ml/s). Check for caval thrombi, position of renal veins and congenital anomalies. Select the optimum level for filter placement and measure the IVC diameter, correcting for magnification (typically 24 percent).
- B. Advance the introducer catheter to the selected level under fluoroscopic control. The guidewire and dilator should be reinserted to facilitate this. For removal insertion, the introducer catheter tip should be 1 cm below the lowest renal vein.
- C. Remove the filter and delivery system from Kit B.
- D. Connect a 500-ml bag of saline to the sideport of the Y-adapter using a standard drip infusion set. Allow the saline infusion to flow around the filter in the storage tube for 5 seconds to soften it for passage through the introducer catheter. Adjust the infusion set to provide a rapid drip rate. Tighten the Luer-Lock adapter valve to minimize reflux of saline, but not so tight as to prevent the pusher wire from advancing freely.

NOTE: It is very important to maintain introducer catheter patency with the saline flush so that the grooved segment that will properly orient the filter legs does not become clogged over. This will interfere with filter deployment.

12. Attach the free end of the filter storage tube to the 7 French catheter already in the vein, allowing the saline infusion to flow into the IVC (for a few seconds). The introducer catheter and filter delivery system should be held in a straight line to minimize friction.

Advancement of Filter, Illustrated



13. Advance the filter by moving the distal pusher wire forward through the introducer catheter, advancing the filter with each forward motion of the pusher wire (Figures A-D). Do not pull back on the pusher wire, only advance the pusher wire forward. For the operator's convenience, the introducer catheter may be loosely held without causing kinking to the introducer material, to facilitate pusher wire handling and advancement.
14. Continue forward motion of the pusher wire until the filter tip advances to the radiopaque marker on the distal end of the introducer catheter. At this point, the pusher wire handle should be adjacent to the Y-adapter.

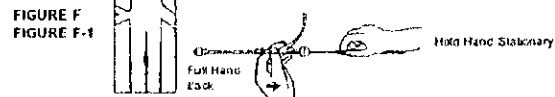
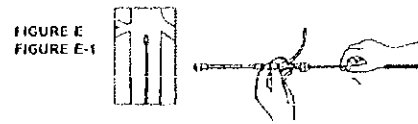
Filter Release/Deployment

15. Deliver and release filter as described below.

Figure E: Fully hold the position in a handle.

Figure E-1: Filter positioned in introducer catheter between the radiopaque markers prior to deployment in IVC.

Filter Release, Illustrated



NOTE: Do not deliver the filter by pushing it beyond the end of the introducer catheter. Instead, unsheath the stationary filter by withdrawing the introducer catheter as described below.

Position the filter tip 1 cm below the lowest renal vein.

Figure F: With one hand held stationary, the other hand draws the Y-adapter and storage tube assembly back completely over the handle, uncovering and releasing the filter.

Figure G-1: Unsheathing of filter in IVC.

Figure G-2: The position of the hands at the completion of the unsheathing process.

Figure G-3: The filter deployed in the IVC.

15. Now withdraw the pusher wire back into the storage tube by first holding the Y-adapter, storage tube, and introducer catheter assembly and pulling back on the pusher wire.

17. Resume the intermittent saline flush or constant drip infusion to maintain introducer catheter patency.

Follow up Venacavogram

18. A follow up venacavogram must be performed after withdrawing the introducer catheter into the filter vein (typically 30 ml of contrast medium at 15 ml/s).

19. Remove the introducer catheter and apply routine compression over the puncture site in the usual way to achieve hemostasis.

K. Warranty

Bard Peripheral Vascular warrants to the first purchaser of this product that this product will be free from defects in materials and workmanship for a period of one year from the date of first purchase and liability under this limited product warranty will be limited to repair or replacement of the defective product, in Bard Peripheral Vascular's sole discretion or refunding your net price paid. Value and less than normal use or defects resulting from misuse of this product are not covered by this limited warranty. TO THE EXTENT ALLOWABLE BY APPLICABLE LAW, THIS LIMITED PRODUCT WARRANTY IS IN LIEU OF ALL OTHER WARRANTIES, WHETHER EXPRESS OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. IN NO EVENT WILL BARD PERIPHERAL VASCULAR BE LIABLE TO YOU FOR ANY INDIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES RESULTING FROM YOUR HANDLING OR USE OF THIS PRODUCT.

Some state/province laws do not allow an exclusion of implied warranties, incidental or consequential damages. You may be entitled to additional remedies under the laws of your state/province. Labeling Issue Date: 12/04

In the event 3 years have elapsed between this date and product use, the user should contact C. R. Bard Inc. to see if additional product information is available.

Bard, Recovery, and Recovery Cone are registered trademarks of C. R. Bard Inc. or an affiliate.

U.S. Patent No. 6,097,558 and 6,252,625, Other Patents Pending

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References

1. Quality Improvement Guidelines for Percutaneous Permanent Inferior Vena Cava Filter Placement for the Prevention of Pulmonary Embolism. Grassi, Omar, Cardella, et al. J Vasc Med Biol 2003; 14:5271-5275

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USA

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1-800-321-4254













FAX: 1-480-955-7462

1-800-440-5176

www.bardpv.com



EEA Authorized Representative
Bard Limited
Crawley, UK
RH11 5UP

	Recovery Filter System	NON-PYROGENIC	Sterile, non-pyrogenic unless package is damaged or opened
	Expiry Date		Warning: After use, this product may be a potential biohazard. Handle and dispose of it accordingly with the accepted medical practice and applicable laws and regulations.
LOT	Lot Number		Contents: Kit A, One (1) FET Intermittent Catheter, One Long with Dome Kit B, One (1) Recovery Filter Forward Delivery System
	Readme, See Information for Use		Bard, Recovery, and Recovery Care are registered trademarks of C.R. Bard Inc. or its affiliates.
STERILE EO	Radically Wet Ethylene Oxide		Protect From Heat
	Do Not Flame - No Hot Objects		Keep Dry
	Do Not Reuse Here		
	Contents Sterile, Unless Package is Damaged or Opened		
	MRI compatible: MRI safe and no adverse interaction with use or affected by the operation of an MRI device.		

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PKS100028 Rev. 01 02/05

Traditional 510(k)
Recovery[®] Filter System

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Draft Promotional Statements

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Recovery[®] Filter System

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Draft Promotional Statements

The following are draft statements that Bard is planning on using in the advertising and promotional materials for the subject device:

- Increased migration resistance (Refer to Table 3)
- This modified Recovery Filter has an improved, robust and stronger design (Refer to Table 3)

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Appendix 2

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Recovery[®] Filter System

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Appendix 2 – Indications for Use Statement

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Recovery® Filter System

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Indications For Use Statement

Device Name: Recovery Filter System

Indications for Use: The Recovery Filter is indicated for use in the prevention of recurrent pulmonary embolism via permanent placement in the vena cava in the following situations:

- Pulmonary thromboembolism when anticoagulants are contraindicated
 - Failure of anticoagulant therapy for thromboembolic disease.
 - Emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced.
 - Chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated.
-

**PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE
ON ANOTHER PAGE IF NEEDED.**

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use _____ OR Over-The-Counter Use _____
(Per 21 CFR 801.109)

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Appendix 3

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Recovery[®] Filter System

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Appendix 3 - Truthful and Accuracy Statement

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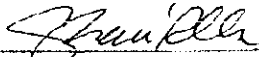
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Recovery[®] Filter System

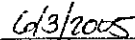
Page 52

Truthful and Accuracy Statement

Pursuant to 21 CFR 807.870, I, Shari L. Allen, certify that to the best of my knowledge and belief based upon the data and information submitted to me in the course of my responsibilities as Director of Regulatory Affairs and Clinical Research at Bard Peripheral Vascular, Inc and reliance thereupon, the data and information submitted in this Traditional 510(k) are truthful and accurate and that no facts material for review of the substantial equivalence of this device have been knowingly omitted from this submission.



Shari L. Allen
Director of Regulatory Affairs and Clinical Research



Date

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Appendix 4

Traditional S10(k)
Recovery[®] Filter System

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Appendix 4. Summary of Safety and Effectiveness

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Recovery[®] Filter System

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Summary of Safety and Effectiveness

As required by the Safe Medical Devices Act of 1990, coded under Section 513, Part (l)(3)(A) of the Food, Drug and Cosmetic Act, a summary of the safety and effectiveness information upon which substantial equivalence determination is based as follows:

A. Submitter Information:

Applicant: Bard Peripheral Vascular, Inc
1625 West 3rd Street
P.O. Box 1740
Tempe, Arizona 85280

Phone: 480-303-2539

Fax: 480-449-2546

Contact: Shari L. Allen, Director of Regulatory Affairs and Clinical Research

B. Subject Device Name: Recovery Filter

Common or Usual Name: Vena Cava Filter

Classification: Class II with Special Controls

The special controls for this device are compliant with the following:

- FDA's "Guidance for Cardiovascular Intravascular Filter 510(k) Submissions", issued on November 26, 1999.
- BS EN 12006-3:1999 entitled, "Non-Active Surgical Implants - Particular Requirements for Cardiac and Vascular Implants - Part 3: Endovascular Devices".

C. Predicate Device

Device Name(s): Recovery Filter System (K022236, cleared 11/27/02)

Classification: Class II with Special Controls

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D. Subject Device Description:

The subject device description is identical to the Recovery Filter System description and indications. The modifications made to the Recovery Filter and delivery system are primarily dimensional. No material changes or additional components have been incorporated.

The predicate filter device has been modified as a result of continued product improvement. The predicate delivery system has been modified to accommodate the geometry modifications of the predicate filter.

E. Statement of Intended Use for Subject Device:

The Recovery Filter is indicated for use in the prevention of recurrent pulmonary embolism via permanent placement in the vena cava in the following situations:

- Pulmonary thromboembolism when anticoagulants are contraindicated.
- Failure of anticoagulant therapy for thromboembolic disease.
- Emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced.
- Chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated.

F. Substantial Equivalence:

The subject device has the following similarities to the predicate device that received clearance to market via K022236 on 11/27/02 and K031328 on 07/25/03:

- Same intended use;
- Same filter and delivery system materials;
- Same operating principle;
- Same fundamental scientific technology;
- Same packaging configuration and materials;
- Same sterility assurance level and method of sterilization.

The design, material, components, fundamental technology and intended use featured with the Recovery Filter System are substantially equivalent to those featured with the predicate Recovery Filter System based on the design verification and validation activities.

Appendix 5

Traditional 510(k)
Recovery[®] Filter System

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Appendix 5 - Engineering Drawings

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Traditional 510(k)
Recovery® Filter System

Subject Device – Filter

(b)(4)

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Traditional 510(k)
Recovery® Filter System

Subject Device

(b)(4)

(b)(4)

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Traditional 510(k)
Recovery® Filter System

(b)
(4)

Predicate Device -

(b)(4)

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Traditional 510(k)
Recovery® Filter System

Predicate Device

(b)
(4)

(b)(4)

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Traditional 510(k)
Recovery[®] Filter with Femoral Delivery

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Appendix 6. – Design Verification and Validation Protocol and Report

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**Traditional 510(k)
Recovery® Filter with Femoral Delivery**

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A copy of the Design Verification and Validation Protocol and Report is provided on the attached CD-ROM.

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BPV-17-01-00125504



Test Protocol Number

TPR-05-01-13

REV 0

**G1A Recovery[®] Filter - Femoral System
Design Verification and Validation Protocol**

Project # 8027

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BPV-17-01-00125505



Test Protocol Number

TPR-05-01-13

REV 0

**G1A Recovery[®] Filter - Femoral System
Design Verification and Validation Protocol**


Project # 8027

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1.0 OBJECTIVE / PURPOSE OF TEST

The objective of this study is to verify and validate the design of the G1A Recovery Filter Femoral System (RF-210F), project # 8027. Design verification testing will consist of the following: dimensional, tensile, leak, marker band security, migration resistance, removal force, and radial strength testing. Design validation testing will consist of evaluating the performance of the entire system, utilizing a simulated use anatomical model (ref. ETR-05-01-07). A chronic (in process) and acute (ETR-05-01-06) animal study were also performed as part of design validation.

NOTE: *Simulated Use testing consists of the following elements: Trackability, Pushability, Flex/Kink, Filter Advancement, Deployment Force, Deployment Accuracy, Filter Fixation, Ability to Deploy, and Deployment Configuration.*

2.0 OVERVIEW / BACKGROUND


The Recovery Filter is a blood clot trapping device designed to prevent pulmonary embolism by mechanical filtration. The filter is implanted percutaneously in the inferior vena cava (IVC). The Recovery Filter has the additional feature of being able to be percutaneously removed after implantation with minimal trauma to the IVC. The Recovery Filter may be used as a permanent filter or be implanted temporarily to treat a temporary risk of pulmonary embolism.

The G1A Recovery Filter (RF-210F) has been modified, in comparison to the current Recovery Filter (RF-048F), to increase migration and fracture resistance, and to minimize the likelihood of leg twisting, appendage snagging, filter tilting, and caval perforation. These changes include an increased ground wire diameter of the hook from 0.0085" to 0.0105" in order to improve the fracture resistance of the hook and to improve the migration resistance of the filter. The leg span has been increased from 32mm to 40mm in order to improve the ability of the filter to expand with a distending vena cava. The total filter arm length has increased from 20mm to 25mm, enlarging the filter arm span from 30mm to 33mm to aid in filter centering. An additional inward bend has been applied to the end of the filter arm in order to improve arm interaction with the vessel wall, to address caval perforations and appendage snagging. The arc of filter arm, as it attaches to the sleeve, has been modified to have a smooth radiused transition instead of sharp angle. This change was made in order to reduce the stress concentration generated by the sharp angle and thus improve fracture resistance in the area of the filter.

Currently, the Recovery Filter (RF-048F) is deployed via a femoral vein approach using a delivery sheath with the filter mounted on a pusher wire. The new delivery system has been modified to increase the delivery sheath distal tip ID (including the distal marker band) from 0.083 +/-0.001" to 0.085+0.002"/-0.000" to allow for ease of delivery of the G1A filter. In addition to the change in sheath tip ID, the OD of the dilator shaft was increased from .079" to .081" to ensure a smooth transition in profile during sheath advancement into the anatomy. Additionally, the mounting spline of the pusher wire has been modified to accommodate the stronger hooks and assist the G1A filter deployment.

The G1A Recovery Filter Femoral System (catalog # RF-210F) consists of a dilator, a 7 French I.D. introducer sheath, and a delivery catheter. The G1A Recovery Filter is preloaded

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within the storage tube of the delivery system, which consists of pusher pad and spline attached to a pusher wire and handle. The Femoral System is packaged in kits. Kit A consists of a dilator and a 7 French introducer sheath. Kit B consists of the delivery system containing the filter placed within a shipping tray. Each Kit is packaged in a separate unit pouch. Both unit pouches are packaged in a final unit pouch.


3.0 TEST METHOD RATIONALE

The following elements are affected by the design changes, per the change summary (ref. Appendix 14) and risk analysis (reference DFMEA070022), and will be evaluated as part of this study:

- Dimensional/Visual Inspection (Pre-Sterile)
 - Filter Arm Span
 - Filter Leg Span
 - Ground Wire Diameter
 - Arm Length
 - Hook Dimensions
 - Introducer Sheath Tip ID
 - Distal & Proximal Marker/Sheath ID
 - Distal & Proximal Marker/Sheath OD
 - Dilator OD
 - Split Spline OD
- Dimensional/Visual Inspection (Post-Sterile)
 - Introducer Sheath Tip ID
 - Distal & Proximal Marker/Sheath ID
 - Distal & Proximal Marker/Sheath OD
 - Dilator ID
 - Dilator OD
 - Spline/Filter Interaction
- Bench Deployment Simulated Use Testing
- Deployment Force Testing
- Post Deployment Dimensions
 - Arm Span
 - Leg Span
- Filter Leg Radial Strength
- Migration Resistance
- Filter Removal Force
- Markerband Security Testing
- Dilator/Hub Joint Tensile Strength Testing
- Spline/Wire Joint Tensile Strength Testing
- Dilator Leakage Testing

The following elements were not affected by the design change, per the change summary (ref. Appendix 14) and risk analysis (reference DFMEA070022), and will not be evaluated as part of this study. Although these elements are not affected, a detailed explanation (i.e., rationale) is warranted to further explain their exclusion from testing, as follows:


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PPS # and Characteristic:

- **6.1.1.1.3 Filter Height** – The G1A (RF-210F) filter height is controlled by the annealing jig and is identical to the predicate device height (RF-048F) when constrained in an IVC lumen up to 28mm in diameter as defined by the IFU. The difference in the nominal height between the filters is due to the difference in the leg span in the unconstrained state. The relationship between the leg span and the height can be described as follows: the longer the leg span (e.g. due to a larger diameter IVC), the shorter the filter height. Therefore, this dimension will not be inspected.
- **6.2.1.1 Filter Clot Capturing Ability** – The filter arm and leg diameters are the same for the G1A Recovery Filter as for the RNF. Therefore, the G1A Recovery Filter luminal cross section is identical to the RNF when deployed in an IVC up to 28mm in diameter as defined by the IFU. Therefore, the filter clot capturing ability has not changed (reference RD-RPT-103) and will not be tested.
- **6.1.3.1 Shelf Life** – The RNF Femoral System has proven it is stable after 3 year accelerated aging per Stability Test Report STR-02-09-01. The materials for the G1A Recovery Filter Femoral System are identical to those used in the RNF. Therefore, the G1A Recovery Filter Femoral System will not require further stability testing and will adopt the 3 year shelf life indication.
- **6.4.1 MRI Compatibility** - The materials used in the G1A Recovery Filter Femoral System are identical to the RF-048F. The MRI testing report ETR-02-12-01 from the RF-048F successfully met the MRI compatibility test requirements. Therefore, the G1A Recovery Filter Femoral System will not require further MRI compatibility testing.
- **6.7.1 Biocompatibility** - The materials used in the G1A Recovery Filter Femoral System are identical to the RF-048F. Therefore, the biological testing reports from the RF-048F will be referenced as the supporting evidence in the Biocompatibility Test Requirements Checklist form FM0700290 resulting in an adoption of the design with no further biological testing. Reference BR-8027 for further details.
- **6.2.2.5 Leading Edge of Dilator/Sheath** - although the dilator increased in OD from 0.079" to 0.081" and the Sheath increased in ID from 0.83" to 0.85" the tolerance stack between the two components (0.004") was maintained from the original design of the RF-048F. Therefore, further testing of this element is not warranted.
- **6.2.4.4 Filter Deployment** - In the original RF-048F PPS (ref. PPS070016) this characteristic addressed the general technique of deployment, stating that it "must be considered simple and require minimal end-user manipulation". The basic method of delivery has not changed with the modified design of the G1A filter and delivery system. Therefore, further testing of this element is not warranted.
- **6.2.4.6 Delivery of Filter through the Femoral Vein** - the intended use and indications for use have not changed with the modified design of the G1A filter and delivery system. Therefore, further testing of this element is not warranted.
- **6.12.1 Labeling Requirements** - The design changes will require a new item number and artwork for the RF-210F. Therefore, new labels will be required for the RF-210F. The new labels must comply with Bard Corporate labeling and format requirements specified in document R-004 prior to approval. Therefore, this protocol and report will not evaluate the labels.
- **6.12.2 Instructions for Use (IFU)** - The design changes will require a new item number and artwork for the RF-210F. Therefore, a new IFU will be required for the RF-210F. The new

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IFU must comply with Bard Corporate IFU requirements specified in document R-004 prior to approval. Therefore, this protocol and report will not evaluate the IFU.

The following elements were not affected by the design change, per the change summary (ref. Appendix 14) and risk analysis (reference DFMEA070022), and will not be evaluated as part of this study. These elements do not warrant further explanation.

PPS # and Characteristic:


- 6.1.1.1.1 Filter Weld Bead Diameter
- 6.1.1.1.2 Filter Weld Bead Height
- 6.1.1.2.1 Introducer Sheath OD
- 6.1.1.2.3 Introducer Sheath Length
- 6.1.1.2.4 Pusher Wire Effective Length
- 6.1.2.1.1 Filter Wire (Material)
- 6.1.2.2.1 Handle (Material)
- 6.1.2.2.2 Pusher Wire (Material)
- 6.1.2.2.3 Catheter (Material)
- 6.1.2.2.4 Dilator (Material)
- 6.1.2.2.5 Introducer Marker Band (Material)
- 6.1.3.2 Filter Tip Radiopacity
- 6.1.3.3 Filter Radiopacity
- 6.1.3.4 Introducer Sheath Surface Finish
- 6.1.3.5 Introducer Marker Band Radiopacity
- 6.2.1.4 Filter Weld Strength/Integrity
- 6.2.2.2 Side port and Flushing Capabilities
- 6.2.2.4 Introducer Sheath and Y-body/Storage Tube Connection
- 6.2.2.6 Introducer Sheath Tensile Strength
- 6.2.2.8 Sheath Hub Strength
- 6.2.2.9 Introducer Sheath Retraction
- 6.2.3.2 Spline & Sheath Proximal Band Alignment
- 6.2.3.4 Pusher Pad Tensile Strength
- 6.2.3.6 Proximal Cylinder Stop and Pusher Wire Joint Tensile Strength
- 6.2.3.7 Pusher Wire Handle Joint Pull Strength
- 6.2.3.8 Pusher Wire Tensile Strength
- 6.2.4.8 Touhy-Borst Nut Tightness
- 6.6.1 0.9% Saline Solution Compatibility
- 6.6.2 Contrast Compatibility
- 6.8.1 Sterility
- 6.9.3 Angiography Suite, ICU or Cath. Lab
- 6.11.1 Product Sterility (Ability of Packaging to Allow/Maintain)
- 6.11.2 Pouch Seal Strength
- 6.11.3 Pouch Seal Visual Integrity
- 6.13.1 Dilator Hub, Introducer Hub and Y-body Side Port Equipment Interaction
- 6.15.1 Product Hazardous Waste Disposal
- 6.15.2 California Prop. 65

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4.0 REFERENCE DOCUMENTS

- 4.1 TPR-04-09-11: Chronic Animal Study (*test report pending*)
- 4.2 ETR-05-01-07: Validation of the Farlow Scientific Inc. Venous Anatomical Model
- 4.3 ETR-05-01-08: G1A Recovery Filter Femoral System Feasibility Test Report
- 4.4 ETR-05-01-06: G1A Recovery Filter Femoral System Acute Animal Study Report
- 4.5 ETR-04-12-15: G1A Recovery Filter Feasibility with Jugular/Subclavian System
- 4.6 ETR-04-10-04: G1A Recovery Filter (0.0105" x 0.060") Feasibility Phase 1
- 4.7 ETR-04-10-21: Removable G1A Filter, Preliminary Acute Animal Study
- 4.8 ETR-04-08-04: Recovery Filter (RF) Arm Fatigue Test Report
- 4.9 ETR-04-06-06: Recovery Filter (RF) Migration Resistance Improvement DOE and Hook Radius Change
- 4.10 TM1133300: Delivery System Component Tensile Test Method
- 4.11 TM1133400: Catheter Leakage Test Method
- 4.12 TM1133100: Vena Cava Filter Deployment Force Test Method
- 4.13 TM1133600: Delivery System Simulated Use Test Method
- 4.14 TM1134800: Migration Resistance
- 4.15 TM1135200: Filter Deployment Force Test
- 4.16 TM1132600: Post Sterile Dimensional Filter Testing
- 4.17 TM1132700: IVC Filter Radial Force Method
- 4.18 TM1134800: Filter Migration Resistance Testing
- 4.19 TM1133800: Recovery Filter Arm Fatigue Test
- 4.20 TM1132900: Recovery Filter Removal Force Test Method
- 4.21 TM1133300: Delivery System Component Tensile Testing
- 4.22 TM1133400: Catheter Leakage Test Method
- 4.23 TM1132600: Filter Dimensional Test
- 4.24 TM25001164: Band/Immobile Tensile Test (*GFO Test Method*)
- 4.25 RNF Fact Book #7081, Volume 1 of 13, Section 3, p 3 of 4
- 4.26 R5530435 BOM/Routing Process Report (*Preliminary DMR*)
- 4.27 RA070025: Risk Assessment of the G1A Recovery Filter Femoral System
- 4.28 DFMEA070022: Design Failure Mode and Effects Analysis of the G1A Recovery Filter Femoral System
- 4.29 PPS070028: G1A Recovery Filter Femoral System PPS

5.0 RESPONSIBILITIES

GFO: Responsible for manufacturing the test samples and performing pre-sterile inspections.

BPV AME: Responsible for coordinating and overseeing the manufacturing and pre-sterile testing of the test samples. Further responsible for providing resources to aid in the completion of the testing indicated in this protocol.


BPV R&D: Responsible for writing, reviewing, and approving the test protocol and report. Further responsible for providing resources to aid in the completion of the testing indicated in this protocol.

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BPV QA: Responsible for reviewing and approving the test protocol and report. Further responsible for providing resource to lead in the completion of the testing indicated in this protocol.

BPV RA: Responsible for reviewing and approving the test protocol and test report.

Covington QA: Responsible for sterilizing the product, environmentally stressing, and shipping simulation of the product.

6.0 TEST MATERIALS

6.1 Number of Samples:

Samples are to be manufactured and packaged according to the procedures outlined in the router R5530435 (preliminary DMR) and are to be representative of future commercial product.

A total of 120 G1A samples, 90 SNF samples and 30 RNF samples (complete finished units) will be evaluated as part of this study.

6.2 Sample Size Rationale:

Sample sizes are based on the need to demonstrate the specified reliability and confidence levels for each PPS Element as defined by the DFMEA. For variable characteristics, the sample sizes take into account the expected means and standard deviations as experienced during testing. For attribute characteristics, the sample sizes are the minimum number of units required without failure to demonstrate the required reliability and confidence. If necessary, additional samples may be added to assist in meeting required reliability and confidence levels.

Sample sizes take into account commonality between tests, where applicable. Where test results from different tests will be pooled, the rationale is that there is no difference in the PPS Element being evaluated regardless of the test method used for filter compression profile, filter migration resistance, filter centering, sheath/introducer kink resistance, dilator removal, pusher rod kink resistance, filter advancement and deployed filter configuration.

Performance data measured by the user on the rating a scale of 1-4 will be treated as attribute data. The minimum acceptable rating is 2 based on the scale below:

- 1 – Unacceptable
- 2 – Acceptable
- 3 – Good
- 4 – Excellent/Exceptional

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Table 6.1 Sample Size and Rationale for Each Test				
PPS Element	Design Characteristic	User Requirement	Engineering Specification	Risk Quad. Acceptance Criteria
6.1.1.1.4	Filter Arm Span	One Size Filter fits into Vena Cava diameters ≤ 28 mm	30 - 35 mm (Pre-Sterile)	3 Variable Data – Statistically meet dimensional specification with 95%/95% conf./rel. (Measured Pre-Sterile) Note: Post 2X Sterile/Environmental Stress/Ship Simulation/Post Deployment for characterization purposes.
Rationale: Specification for pre-sterile arm span was derived from statistical analysis of filters used in the chronic animal study documented in Lab Notebook 7032 pgs46-51. Therefore, this specification will be evaluated as part of the DV&V testing. Additionally, the Post 2X Sterile/Environmental Stress/Ship Simulation/Post Deployment dimensions will be recorded for informational purposes only, as dimensional verification is already captured by many of the performance tests (i.e., Migration Resistance) during the course of the DV&V testing.				
6.1.1.1.5	Filter Leg Span	One Size Filter fits into Vena Cava diameters ≤ 28 mm	38 - 42 mm (Pre-Sterile)	3 Variable Data – Statistically meet dimensional specification with 95%/95% conf./rel. (Measured Pre-Sterile) Note: Post 2X Sterile/Environmental Stress/Ship Simulation/Post Deployment for characterization purposes.
Rationale: Specification for pre-sterile leg span was derived from statistical analysis of filters used in the chronic animal study documented in Lab Notebook 7032 pgs46-51. Therefore, this specification will be evaluated as part of the DV&V testing. Additionally, the Post 2X Sterile/Environmental Stress/Ship Simulation/Post Deployment dimensions will be recorded for informational purposes only, as dimensional verification is already captured by many of the performance tests (i.e., Migration Resistance) during the course of the DV&V testing.				
6.1.1.1.6	Filter Compression Profile	The filter is deliverable through a 7 Fr ID introducer sheath.	Filter must be deliverable through $0.085" \pm 0.002"$ ID sheath.	2 Attribute Data -- All units must be deliverable through the introducer sheath by the user (Minimum Rating of 2 on a Scale of 1-4) for a statistically valid sample size to meet or exceed 95%/90% conf./rel. Minimum sample size of $n = 30$ (Measured Post 2X Sterile/Environmental Stress/Ship Simulation) Note: Data from Deployment Force Testing ($n=30$) and Simulated Use Testing ($n=60$) will be pooled for this Design Characteristic.
Rationale: The ID of the delivery sheath/hub/tip components covers a range of $0.085" \pm 0.002"$. Also, the profile of the filter has been altered due to the new loading of the filter. Therefore, this specification will be evaluated as part of the DV&V testing.				

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Table 6.1 Sample Size and Rationale for Each Test				
PPS Element	Design Characteristic	User Requirement	Engineering Specification	Risk Quad. Acceptance Criteria
6.1.1.2.2	Dilator ID	The dilator must be 0.038" Guidewire compatible.	0.041" \pm 0.002"	Attribute Data -- All units must pass a Min Pin Gauge for a statistically valid sample size to meet or exceed 95%/90% conf./rel. Minimum sample size of n=30 (Measured Post 2X Sterile/Environmental Stress/Ship Simulation)
Rationale: The OD of the dilator component was increased and required a new extrusion. The new extrusion may have an impact on the dilator ID. Therefore, this specification will be evaluated as part of the DV&V testing.				
6.2.1.2 (Part 1)	Filter Migration Resistance	Migration resistance of G1A must be statistically equivalent to or greater than that of SNF filter.	Migration resistance of G1A in simulated IVC diameters of 15 mm and 28 mm must be statistically equivalent to or greater than that of SNF filter.	Variable Data -- Statistically equivalent or greater migration resistance than that of the SNF with 95%/95% conf./rel. (T-test). Measured Post 2X Sterile/Environmental Stress/Ship Simulation and Post Deployment
6.2.1.2 (Part 2)	Filter Migration Resistance	Migration resistance of G1A must be statistically equivalent to or greater than that of SNF filter.	Standard deviation of G1A results in simulated IVC diameters of 15 mm and 28 mm must be statistically equivalent to or smaller than that of SNF filter.	Variable Data -- Statistically equivalent or less variance in migration resistance than that of the SNF with 95%/95% conf./rel. (F-test). Measured Post 2X Sterile/Environmental Stress/Ship Simulation and Post Deployment
6.2.1.2 (Part 3)	Filter Migration Resistance	Migration resistance of G1A must be statistically equivalent to or greater than that of SNF filter.	G1A must withstand a minimum of 50 mmHg pressure in simulated IVC diameters of 15 mm and 28 mm.	Attribute Data -- All units must withstand a minimum pressure value of 50mmHg for migration resistance (Pass/Fail) for a statistically valid sample size to meet or exceed 95%/95% conf./rel. Minimum sample size of n = 60 (Measured Post 2X Sterile/Environmental Stress/Ship Simulation) Note: Data from 15mm IVC (n=30) and 28mm IVC (n=30) will be pooled for this Design Characteristic.

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Table 6.1 Sample Size and Rationale for Each Test				
PPS Element	Design Characteristic	User Requirement	Engineering Specification	Risk Quad. Acceptance Criteria
6.2.1.2 (Part 4)	Filter Migration Resistance	Migration resistance of G1A must be statistically equivalent to or greater than that of SNF filter.	Migration resistance of G1A in simulated IVC diameter of 32 mm (simulated distended Cava, outside of the indicated range) must be statistically equivalent to or greater than that of SNF filter.	Variable Data – Statistically equivalent or greater migration resistance than that of the SNF with 95%/95% conf./rel. (Measured Post 2X Sterile/Environmental Stress/Ship Simulation and Post Deployment)
Rationale: Specification for filter migration resistance was derived from statistical analysis of filter migration data from engineering report ETR-04-10-04. Therefore, this specification will be evaluated as part of the DV&V testing.				
6.2.1.3	Filter Radial Strength	Filter must not perforate the vessel.	G1A radial strength (legs) must be statistically equivalent or less than that of SNF (legs) in 15 mm simulated IVC.	Variable Data – Statistically equivalent or less radial strength than that of the SNF with 95%/95% conf./rel. (Measured Post 2X Sterile/Environmental Stress/Ship Simulation and Post Deployment)
Rationale: This specification was taken from the RNF PPS070016. The leg span was increased and may affect the radial strength. Therefore, this specification will be evaluated as part of the DV&V testing.				
6.2.1.5	Filter Hook Creep	The filter hook must not be permanently deformed as a result of being constrained in the storage tube for a period of time.	There must be no increasing trend in creep.	G1A hook stress as determined by a finite element analysis model must not be greater than that of the predicate device hook stress.
Rationale: This specification was taken from the RNF PPS070016. The RF-048F hook was found not to creep under the loading stress created when constrained within the storage tube and during delivery. A finite element analysis (FEA) has been performed in order to compare the stress of the hook in the RF-210F and RF-048F while in the storage tube and during deployment (ETR-05-02-02). Therefore, the requirements of this specification will be addressed via the hook stress being less than or equal for the RF-210F than that of the RF-048F as indicated by the FEA.				

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Table 6.1 Sample Size and Rationale for Each Test				
PPS Element	Design Characteristic	User Requirement	Engineering Specification	Risk Quad. Acceptance Criteria
6.2.1.6	Filter Respiratory Fatigue Resistance	The filter must not fracture as a result of corrosives or cyclic stresses within the body.	There must be no fractures of filter elements (arms or legs) due to the cycling of an equivalence of 10 years of pulmonary output (32 million cycles) in a corrosive environment.	3 Filter arm and leg stress as determined by a finite element analysis model must not be greater than that of the predicate device.
Rationale: This specification was taken from the RNF PPS070016. The RF-048F met the cyclic fatigue specification. A finite element analysis (FEA) has been performed (ETR-05-02-02) in order to compare the stresses of the RF-210F and RF-048F while in the storage tube, during delivery and under caval deformation. Therefore, the requirements of this specification will be addressed via the stress being less than or equal for the RF-210F to that of the RF-048F as indicated by the FEA.				
6.2.1.7	Filter Diaphragmatic Fatigue Resistance	Filter arms must have higher fatigue fracture resistance when subjected to biomechanical cyclic stresses as compared to the RF-048F.	Arm fatigue resistance of G1A must be statistically greater than that of the predicate device.	3 Variable Data -- Statistically greater than that of the RN = with 95%/95% conf./rel. (Measured Post 2X Sterile/Environmental Stress/Ship Simulation and Post Deployment)
Rationale: This specification was derived from a requirement to improve arm fatigue resistance over the RF-048F. The arm at sleeve curvature was modified to decrease the stress at this point. Since the RF-048F met the fatigue resistance specification from 6.2.1.3, an improved fatigue resistance could not be shown using the existing test method. Therefore, a new test method was developed in order to demonstrate the arm fatigue capabilities the RF-048F and RF-210F filters. Therefore, this specification will be evaluated as part of the DV&V testing.				

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Table 6.1 Sample Size and Rationale for Each Test				
PPS Element	Design Characteristic	User Requirement	Engineering Specification	Risk Quad.
6.2.1.8	Filter Centering	The filter must self-center within the inferior vena cava.	The filter sleeve must be at a minimum distance of 1/3 the IVC radius from the vessel wall.	3
Rationale: This specification was taken from the RNF PPS070016. The arm span, arm at sleeve curvature was modified and the leg span was increased. Both of these changes may affect the filter centering. Therefore, this specification will be evaluated as part of the DV&V testing. Template for the specified cava diameters have been developed with rings indicating the pass/fail areas.				
6.2.1.9	Filter Removal Force	Minimal force is required to collapse the filter from the deployed state into the RC-15 Recovery Cone catheter.	< 5 lbf. Tensile	3
Rationale: Specification for filter removal force was derived from PPS070016 Recovery Cone System specification of "Force to Separate Cone from Captured Filter" > 5lbf. Therefore, this specification will be evaluated as part of the DV&V testing.				
6.2.2.1	Kink Resistance	Sheath and Introducer should resist kinking and crushing during use.	Sheath and Introducer must resist kinking and crushing in a bench top simulated use test (model # 335-2222).	2
Rationale: This specification was taken from the RNF PPS070016. The introducer OD was increased for the RF-210F. This change may increase the stiffness of the system and may affect the kink resistance. Therefore, this specification will be evaluated as part of the DV&V testing during simulated use testing. The simulated use model for this evaluation is validated anatomical model that was derived from a human cadaver (Ref. ETR-05-01-07).				

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PPS Element	Design Characteristic	User Requirement	Engineering Specification	Risk Quad.	Acceptance Criteria
6.2.2.3	Dilator Removal	The dilator must be able to be removed with a force rated as acceptable by the user.	The dilator must be able to be removed with force rated as acceptable by the user in a bench top simulated use test (model # 335-2222).	2	<p>Attribute Data -- The dilator must be able to be removed with force rated as acceptable (Minimum Rating of 2 on a Scale of 1-4) by the user for a statistically valid sample size to meet or exceed 95%/90% conf./rel.</p> <p>Minimum sample size of n = 30</p> <p>(Measured Post 2X Sterile/Environmental Stress/Ship Simulation)</p> <p>Note: Data from Deployment Force Testing (n=30) and Simulated Use Testing (n=50) will be pooled for this Design Characteristic.</p>
6.2.2.7	Dilator Hub Strength	Minimum strength for dilator and hub joint is 5 lb.	≥ 5 lbf. Tensile	2	<p>Variable Data -- The Dilator to Hub joint tensile strength must be statistically greater than or equal the specification of 5 lbf with 95%/90% conf./rel.</p> <p>(Measured Post 2X Sterile/Environmental Stress/Ship Simulation)</p>
6.2.2.10	Dilator to Hub Joint	Dilator to hub joint must not leak.	Must not leak when 45 psi is applied for 30 seconds (reference ISO 10555-1:1995(E) Annex C test method for liquid leakage under pressure).	2	<p>Attribute Data -- The dilator to hub joint must not leak when 45 psi is applied for 30 seconds (Pass/Fail) for a statistically valid sample size to meet or exceed 95%/90% conf./rel.</p> <p>Minimum sample size of n = 30</p> <p>(Measured Post 2X Sterile/Environmental Stress/Ship Simulation/Post Deployment)</p>
Rationale:	This specification was taken from the RNF PPS070016. The introducer OD was increased for the RF-210F. This change affects the interface between the shaft and over-molded hub. Therefore, this specification will be evaluated as part of the DV&V testing.	The introducer OD was increased for the RF-210F. This change affects the interface between the shaft and over-molded hub. Therefore, this specification will be evaluated as part of the DV&V testing.	The introducer OD was increased for the RF-210F. This change affects the interface between the shaft and over-molded hub. Therefore, this specification will be evaluated as part of the DV&V testing.		

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PPS Element	Design Characteristic	User Requirement	Engineering Specification	Risk Quad.	Acceptance Criteria
6.2.2.11	Marker Band Security	Marker band must remain secure.	Marker band must remain secure when the sheath is placed under 5 lbf tensile load.	2	Attribute Data – The marker band must remain secure when the sheath is placed under a 5lbf tensile load (Pass/Fail) for a statistically valid sample size to meet or exceed 95%/90% conf./rel. Minimum sample size of n = 30 (Measured Post 2X Sterile/Environmental Stress/Ship Simulation and Post Deployment)
Rationale: The delivery sheath ID under the marker bands was increased for the RF-210F by increasing the mandrel OD used during marker band swaging. This change affects the interface between the delivery sheath and swaged marker bands. Therefore, this specification will be evaluated as part of the DV&V testing.					
6.2.3.1	Kink Resistance	The pusher rod must resist kinking and crushing.	The pusher wire must resist kinking and crushing in a bench top simulated use test (model # 335-2222).	2	Attribute Data – The Pusher Rod must resist kinking and crushing (Pass/Fail) for a statistically valid sample size to meet or exceed 95%/90% conf./rel. Minimum sample size of n = 30 (Measured Post 2X Sterile/Environmental Stress/Ship Simulation) <i>Note: Data from Deployment Force Testing (n=30) and Simulated Use Testing (n=60) will be pooled for this Design Characteristic.</i>
Rationale: This specification was taken from the RNF PPS070016. The filter loading configuration was changed for the RF-210F. This change may increase the delivery force of the system and affect the kink resistance. Therefore, this specification will be evaluated as part of the DV&V testing during simulated use testing. The simulated use model for this evaluation is validated anatomical model that was derived from a human cadaver.					
6.2.3.3	Pusher Wire Assembly Radiopacity	The pusher pad and spline must have acceptable radiopacity near the distal end.	The pusher pad and spline must have radiopacity near the distal end rated as acceptable by a physician based on animal study.	3	This Design Characteristic was successfully tested during the Animal Model Evaluation (ETR-05-01-06)
Rationale: This specification was taken from the RNF PPS070016. The spline dimensions were changed for the RF-210F. These changes may affect the radiopacity of the spline. Therefore, this specification was evaluated and deemed acceptable per Acute Animal Report ETR-05-01-08. There were 11 samples viewed under fluoroscopy during the animal study. All were deemed visible by the physician. The radiopacity is a function of material density and thickness. The DFMEA risk Quadrant stipulates 95%/95% n=60 for this characteristic. However, due to the fact that the material and dimensional characteristics of the spline are controlled per the incoming inspection requirements, it is not necessary to further evaluate an additional 49 samples.					

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Table 6.1 Sample Size and Rationale for Each Test				
PPS Element	Design Characteristic	User Requirement	Engineering Specification	Risk Quad. Acceptance Criteria
6.2.3.5	Spline and Pusher Wire Joint Tensile Strength	Spline joint must have a tensile strength exceeding what the system will be exposed to during use before breaking from the wire.	≥ 5 lbf. Tensile	3 Variable Data – The Pusher Wire to Spline joint tensile strength must be statistically greater than or equal the specification of 5 lbf with 95%/95% conf./rel. (Measured Post: 2X Sterile/Environmental Stress/Ship Simulation/Post Deployment)
Rationale: Specification for spline to pusher wire tensile strength was established to accommodate the filter deployment force. The filter deployment force was derived from statistical analysis of filter data from Feasibility Report ETR-05-01-08. Therefore, this specification will be evaluated as part of the DV&V testing.				
6.2.4.1	Filter Deployment Accuracy	The user must be able to accurately deploy the filter in a bench top simulated use test.	± 10 mm (Deployed in a bench top simulated use model # 335-2222).	3 Attribute Data – The user must be able to accurately deploy the filter within 10mm of the intended target (Pass/Fail) for a statistically valid sample size to meet or exceed 95%/95% conf./rel. Minimum sample size of: n = 60 (Measured Post 2X Sterile/Environmental Stress/Ship Simulation)
Rationale: This specification was taken from the RNF PPS070016. The filter loading configuration, arm span, leg span, spline design and sheath tip ID were changed for the RF-210F. These changes may affect the filter deployment accuracy. Therefore, this specification will be evaluated as part of the DV&V testing during simulated use testing. The simulated use model for this evaluation is validated anatomical model that was derived from a human cadaver. This test will use a latex deployment tube to more accurately simulate the elastic response of IVC tissue than the rigid silicone tube.				
6.2.4.2	Deployment Force	The user must be able to deploy the filter with minimal force.	≤ 5 lbf	2 Variable Data – The force required to deploy the filter must be statistically less than or equal the specification of 5 lbf with 95%/90% conf./rel. (Measured Post 2X Sterile/Environmental Stress/Ship Simulation)
Rationale: The specification for filter deployment force was derived from statistical analysis of filter data from Feasibility Report ETR-05-01-08 and physician feedback from Animal Model Evaluation (ETR-05-01-06). Therefore, this specification will be evaluated as part of the DV&V testing.				

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PPS Element	Design Characteristic	User Requirement	Engineering Specification	Risk Quad.	Acceptance Criteria
6.2.4.3	Filter Advancement:	The user must be able to advance the filter through the delivery system.	The user must be able to advance the filter through the delivery system with a force rated acceptable in a bench top simulated use test (model # 335-2222).	2	<p>Attribute Date – The user must be able to advance the filter from the storage tube and through the introducer sheath with force rated as acceptable (Minimum Rating of 2 on a Scale of 1-4) by the user for a statistically valid sample size to meet or exceed 95%/90% conf./rel.</p> <p>Minimum sample size of n = 30</p> <p>(Measured Post 2X Sterile/Environmental Stress/Ship Simulation)</p> <p>Note: Data from Deployment Force Testing (n=30) and Simulated Use Testing (n=60) will be pooled for this Design Characteristic.</p>
<p>Rationale: This specification was taken from the RNF PPS070016. The filter loading configuration, arm span, leg span and spline design were changed for the RF-210F. These changes may affect the filter advancement through the system. Therefore, this specification will be evaluated as part of the DV&V testing during simulated use testing. The simulated use model for this evaluation is validated anatomical model that was derived from a human cadaver.</p>	Deployed Filter Configuration	The filter must deploy with no arm and/or leg entanglement.	The filter must deploy with no arm and/or leg entanglement in a bench top simulated use test (model # 335-2222, 28 mm Cave).	3	<p>Attribute Date – The filter must deploy with no arm and/or leg entanglement for a statistically valid sample size to meet or exceed 95%/95% conf./rel.</p> <p>Minimum sample size of n = 60</p> <p>(Measured Post 2X Sterile/Environmental Stress/Ship Simulation/Post Deployment)</p> <p>Note: Data from Deployment Force Testing (n=30) and Simulated Use Testing (n=60) will be pooled for this Design Characteristic.</p>
6.2.4.5					
<p>Rationale: This specification was taken from the RNF PPS070016. The ID under the marker bands, loading profile, arm span, leg span and spline design were changed for the RF-210F. These changes may affect the filter deployment configuration. Therefore, this specification will be evaluated as part of the DV&V testing during simulated use testing. The simulated use model for this evaluation is validated anatomical model that was derived from a human cadaver.</p>					

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Table 6.1 Sample Size and Rationale for Each Test				
PPS Element	Design Characteristic	User Requirement	Engineering Specification	Risk Quad. Acceptance Criteria
6.2.4.7	Filter Centering	The delivery system must be capable of deploying the filter such that the sleeve would be at the minimum distance of 1/3 IVC radius from the vessel wall.	The delivery system must be capable of deploying the filter such that the filter sleeve would be at the minimum distance of 1/3 IVC radius from the vessel wall in a bench top simulated use test (model # 335-2222, 28 mm Cava).	3 Same as PPS Element 6.2.1.8.
Rationale: This specification was taken from the RNF PPS070016. The ID under the marker bands, loading profile, arm span, leg span and spline design were changed for the RF-210F. These changes may affect the filter centering. Therefore, this specification will be evaluated as part of the DV&V testing during simulated use testing. The simulated use model for this evaluation is validated anatomical model that was derived from a human cadaver.				
6.2.4.9	Filter Hook and Spline Interaction	Filter hooks must not dislodge from the spline during shipping or handling.	Filter hooks must not dislodge from the spline during shipping or handling.	2 Attribute Data – The Filter hooks must not dislodge from the spline during shipping or handling for a statistically valid sample size to meet or exceed 95%/90% conf./rel. Minimum sample size of n = 30 (Measured Post 2X Sterile/Environmental Stress/Ship Simulation)
Rationale: This specification was taken from the RNF PPS070016. The filter loading configuration, arm span, leg span and spline design were changed for the RF-210F. These changes may affect the filter hook and spline interaction. Therefore, this specification will be evaluated as part of the DV&V testing prior to simulated use testing.				
6.8.2	Number of Exposures	The delivery system must be able to be sterilized a minimum of two cycles.	Delivery system is functional after 2X EtO	1 All test samples for this protocol will be 2X EtO sterilized. Therefore, this PPS Element will Pass or Fail based on acceptability of the previously specified PPS Elements. 95%/85% conf./rel. Minimum sample size of n = 18 (Measured Post 2X Sterile/Environmental Stress/Ship Simulation and Post Deployment)

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Table 6.1 Sample Size and Rationale for Each Test				
PPS Element	Design Characteristic	User Requirement	Engineering Specification	Risk Quad. Acceptance Criteria
Rationale: This specification was taken from the RNF PPS070016. The filter loading configuration, arm span, leg span and spline design were changed for the RF-210F. These changes may be effected by sterilization. Therefore, all units will be subjected to 2X EIO in order to evaluate the effects of 2X EIO on the device as part of the DV&V testing.				
6.9.1	Warehouse Environment	Product must be functional after being subjected to warehouse environmental conditions.	Product must satisfy TM0358, TM0035 (Covington), 62.8 C for 24hrs.	1 All test samples for this protocol will be subjected to thermal cycling representative of the anticipated warehouse environment. Therefore, this PPS Element will Pass or Fail based on acceptability of the previously specified PPS Elements. 95%/85% conf./rel. Minimum sample size of n = 18 (Measured Post 2X Sterile/Environmental Stress/Ship Simulation and Post Deployment)
Rationale: This specification was taken from the RNF PPS070016. The filter loading profile, arm span, leg span and spline design were changed for the RF-210F. These changes may be effected by thermal cycles during storage. Therefore, all units will be subjected to thermal cycling in order to evaluate the effects of anticipated storage temperature on the device as part of the DV&V testing.				
6.9.2	Truck / Air Transport	Product must be functional after being transported.	Product must satisfy TM0358 (Covington).	1 All test samples for this protocol will be subjected to transportation simulation that is representative of anticipated truck and air transportation. Therefore, this PPS Element will Pass or Fail based on acceptability of the previously specified PPS Elements. 95%/85% conf./rel. Minimum sample size of n = 18 (Measured Post 2X Sterile/Environmental Stress/Ship Simulation and Post Deployment)
Rationale: This specification was taken from the RNF PPS070016. The filter loading configuration, arm span, leg span and spline design were changed for the RF-210F. These changes may be effected by forces encountered during shipping. Therefore, all units will be subjected to transportation simulation in order to evaluate the effects of anticipated shipping forces on the device as part of the DV&V testing.				

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Table 6.1 Sample Size and Rationale for Each Test				
PPS Element	Design Characteristic	User Requirement	Engineering Specification	Risk Quad. Acceptance Criteria
None	Ground Wire Diameter	N/A	0.0105" ± 0.0005" (Pre-Sterile)	3 Variable Data – Statistically meet dimensional specification of 0.0105" ± 0.0005" with 95%/95% conf./rel. (Measured Pre-Sterile)
Rationale: This specification is critical to the design of the G1A Recovery Filter. Therefore, units will be evaluate pre-sterile as part of the DV&V testing.				
None	Arm Length	N/A	18.75mm ± 1mm (Pre-Sterile)	3 Variable Data – Statistically meet dimensional specification of 18.75mm ± 1mm with 95%/95% conf./rel. (Measured Pre-Sterile)
Rationale: This specification is critical to the design of the G1A Recovery Filter. Therefore, units will be evaluate pre-sterile as part of the DV&V testing.				
None	Hook Dimensions	N/A	Must meet template Template TA-8004-1024 (Pre-Sterile)	3 Attribute Data – The Filter hooks must be within the limits of the hook template for a statistically valid sample size to meet or exceed 95%/95% conf./rel. Minimum sample size of n = 60 (Measured Pre-Sterile)
Rationale: This specification is critical to the design of the G1A Recovery Filter. Therefore, units will be evaluate pre-sterile as part of the DV&V testing.				
None	Introducer Sheath Tip Inner Diameter	N/A	0.085" ID Min	3 Attribute Data – The Sheath Tip ID must accept a 0.083" pin gage (Pass/Fail) for a statistically valid sample size to meet or exceed 95%/95% conf./rel. Minimum sample size of n = 60 (Measured Pre-Sterile and Post 2X Sterile/Environmental Stress/Ship Simulation)
Rationale: This specification is critical to the design of the delivery system. Therefore, units will be evaluated as part of the DV&V testing.				
None	Introducer Sheath Inner Diameter under Distal and Proximal Swaged Marker Bands	N/A	0.083" ID Min	3 Attribute Data – The Sheath ID under the Distal and Proximal Marker Bands must accept a 0.083" pin gage (Pass/Fail) for a statistically valid sample size to meet or exceed 95%/95% conf./rel. Minimum sample size of n = 60 (Measured Pre-Sterile and Post 2X Sterile/Environmental Stress/Ship Simulation)

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Table 6.1 Sample Size and Rationale for Each Test				
PPS Element	Design Characteristic	User Requirement	Engineering Specification	Risk Quad. Acceptance Criteria
Rationale: This specification is critical to the design of the delivery system. Therefore, units will be evaluated as part of the DV&V testing.				
None	Distal Swaged Marker Band Outer Diameter	N/A	$0.118" \pm 0.002"$	2 Variable Data – Statistically meet dimensional specification of $0.118" \pm 0.002"$ with 95%/90% conf./rel. (Measured Pre-Sterile and Post 2X Sterile/Environmental Stress/Ship Simulation)
Rationale: This specification is critical to the design of the delivery system. Therefore, units will be evaluated as part of the DV&V testing.				
None	Proximal Swaged Marker Band Outer Diameter	N/A	$0.118" \pm 0.002"$	2 Variable Data – Statistically meet dimensional specification of $0.118" \pm 0.002"$ with 95%/90% conf./rel. (Measured Pre-Sterile and Post 2X Sterile/Environmental Stress/Ship Simulation)
Rationale: This specification is critical to the design of the delivery system. Therefore, units will be evaluated as part of the DV&V testing.				
None	Dilator Outer Diameter	N/A	$0.081" \pm 0.002"$	2 Variable Data – Statistically meet dimensional specification of $0.081" \pm 0.002"$ with 95%/90% conf./rel. (Measured Pre-Sterile and Post 2X Sterile/Environmental Stress/Ship Simulation)
Rationale: This specification is critical to the design of the delivery system. Therefore, units will be evaluated as part of the DV&V testing.				
None	Split Spine Outer Diameter	N/A	$0.081" \pm 0.001"$ (Pre-Sterile)	3 Variable Data – Statistically meet dimensional specification of $0.081" \pm 0.001"$ with 95%/95% conf./rel. (Measured Pre-Sterile)
Rationale: This specification is critical to the design of the delivery system. Therefore, units will be evaluated as part of the DV&V testing.				

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6.3 Sample identification:

Samples will be labeled following removal from packaging in sequential order (ref. Section 9.2 for further details).

7.0 SAMPLE PRECONDITIONING AND TEST ENVIRONMENT

All samples will be sent to Covington, GA for 2x EO cycle 7 sterilization.

Thereafter, all samples will be environmentally stressed using the following procedures outlined in TM0635 (Covington document).

- Perform accelerated age testing at 62.8 °C for 24 hours per section 6.2 in TM0635.
- Perform environmental stress conditioning for 24 hours per section 6.3.3 in TM0635.
- Allow product to stabilize at room temperature for 24 hours (not outlined in TM0635).

Finally, perform ship testing on all samples per TM0358 (Covington document). The following is a list of all samples with quantity.

- G1A finished units (120)
- SNF finished units (90)
- RNF finished units from inventory (30)

The test methods outlined within this test protocol will be followed in regards to further sample preconditioning and testing environment. Testing will occur at Bard Peripheral Vascular.

8.0 EQUIPMENT LIST

Reference each specific test method for equipment list (reference sections 4.10-4.18).

9.0 TEST PROCEDURE

NOTE: Reference Appendix 1.1 for the Test Plan Flowchart that displays the order of testing.


9.1 Pre-Sterile Dimensional/Visual Inspection (G1A Only)

Table 6.1 outlines the pre-sterile dimensional/visual inspection data that needs to be recorded for samples 1-120 during the manufacturing process along with procedure additions/deviations. In some cases, the incoming inspection record will satisfy the requirement and may be attached (reference table 2).

The following dimensions will be inspected during IQC/manufacturing:

- o Leg Span (Mfg.)

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- Ground Wire (IQC)
- Arm Length (Mfg.)
- Arm Span (Mfg.)
- Hook Dimensions (Mfg.)
- Introducer Sheath Tip ID (IQC)
- Distal & Proximal Marker/Sheath ID (Mfg.)
- Distal & Proximal Marker/Sheath OD (Mfg.)
- Dilator OD (IQC)
- Split Spline OD (IQC)

Post manufacturing, all G1A samples are to be 2x EO sterilized, environmentally stressed, and ship tested (reference section 7.0).

9.2 Sample Identification

All sample units

Upon receipt of the test samples label all parts of the system with the same identification number in chronological order as you inspect them using a Sharpie. Use the following number scheme for all samples

- Simon Nitinol Units (SF1 thru SF90)
- Recovery Filter Units (RF1 thru RF30)
- G1A units (G1A1 thru G1A120)

NOTE: For the G1A units perform 9.2 and 9.3 simultaneously. Do not test per section 9.3 for SF and RF units.

9.3 Spline & Hook Engagement Integrity

G1A units (G1A1 thru G1A120)

After issuing a sample identification number for the G1A units hold the storage tube of the delivery system in your hand and rotate the system 360 degrees. As you are rotating the system inspect the filter hooks and spline interaction. Note any instances of filter/spline separation on the data sheet in Appendix 2.1

9.4 Post-Sterile Dimensional Testing (Delivery System)

G1A units (G1A1 thru G1A60)


Using a 0.085" pin gage, inspect the Introducer Sheath tip ID and fill out the data sheet in Appendix 2.2.

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Hold the Introducer Sheath in the vertical position with distal end facing the floor. Advance a 0.083" pin gage from the proximal end to the distal end and inspect the proximal and distal marker band ID's. Fill out the data sheet in Appendix 2.2

Using a 0.038" pin gage, inspect the Dilator Tip ID and fill out the data sheet in Appendix 2.2.

G1A units (G1A61 thru G1A90)

Using a laser mic record the OD of a calibrated 0.085" pin gage. Rotate the pin gage 90 degrees and record the OD of the same pin gage. Use the laser mic to record the distal and proximal marker band OD's on the Introducer Sheath and the dilator OD at the largest section of the tapered end. To obtain these OD measurements perform the following steps:

- Take 2 measurements, 90 degrees apart, of each dimension and record the outputted average of these measurements from the laser mic. Record data to 3 decimal digits.

9.5 **Bench Top Simulated Use Testing**

G1A units (G1A1-G1A120)

Perform the Simulated Use Testing per TM1133600, Draft (Appendix 3) on samples G1A units.

NOTE: The following special instructions

- **Samples G1A1-G1A30 & G1A91-G1A120:** Use 28mm latex tubing (Make sure to record tubing lot number on the data collection form). **NOTE:** Skip steps 6 and 7 in TM1133600.
- **Samples G1A31-G1A60 & G1A61-G1A90:** Use 21mm silicone tubing. Stop following TM1133600 at procedure step 10 and continue on to section 9.5.

9.6 **Deployment Force Testing**

G1A units (G1A31-G1A60 & G1A61-G1A90)

Perform the Filter Deployment Force Testing per TM1135200 beginning at step 9 (Appendix 4) and replace step 13 with the following step:


Visually inspect the deployed device in the model. Note the conformance of the device to the vessel wall, the deployment configuration, and any other appropriate observations (e.g. kinks, bends, twisting, component separation, or

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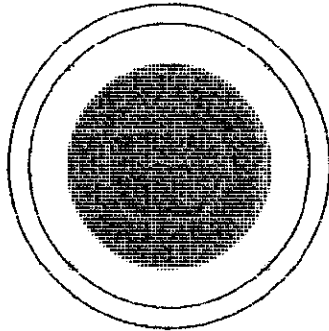
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damage). Record any observations in the comment section of the data collection form.

With the device still deployed record whether or not the deployment configuration was acceptable.

The acceptable configuration is as follows:

- 1.) No legs of the filter are crossed.
- 2.) Using the deployment template (T1181100), the filter sleeve is within the shaded region of the diagram below:



9.7 Radial Strength Arm/Leg Testing (Filter)

G1A units (G1A1-G1A30)

SF units (SF1-SF30)

Perform the Radial Strength Testing per TM11327000 (Appendix 6) for G1A and SNF filter samples in a 15mm clamshell:

- Leg Radial Force for G1A1-G1A30
- Leg Radial Force for SNF samples (SF31-SF60)

9.8 Post-Sterile Dimensional Testing (Filter)

G1A units (G1A31-G1A60)


Inspect the post-sterile units for G1A units per TM1132600 Appendix 5.

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9.9 **Migration Resistance Testing (Filter)**

Perform the Migration Resistance Testing per TM1134800 (Appendix 7) for the following IVC sizes in the following tube order. Refer to Appendix 13 for the randomized run matrix.

- 15mm IVC (G1A1-G1A30, SF1-S30) use small sausage casing
- 28mm IVC (G1A31-G1A60, SF31-S60, RF1-R30) use large sausage casing
- 32mm IVC (G1A61-G1A90, SF61-S90) use large sausage casing

NOTE: Use the Recovery Cone to deploy filters. Ensure hooks stay outside of loading tube.

9.10 **Arm Bend Fatigue Testing (Filter)**

G1A units (G1A31-G1A60)
RF units (RF1-RF30)

Perform the Arm Bend Fatigue Testing per TM1133800 (Appendix 8) on the G1A and RF samples.

9.11 **Removal Force Testing (Filter)**

G1A units (G1A91-G1A120)

Perform the Removal Force Testing per TM1132900 (Appendix 9) for G1A units.

9.12 **Marker Band Security Testing (Sheath)**

G1A units (G1A1-G1A30)

Perform the Marker Band Security Testing per TM25001164 (Appendix 10) for G1A sheath samples on the proximal marker band only.

9.13 **Dilator/Hub and Spline/Wire Tensile Testing**

G1A units (G1A1-G1A30)

Perform the Delivery System Component Tensile Testing per TM1133300 (Appendix 11) for the G1A dilator samples using test fixtures T1165900 and T1166282.


Perform the Delivery System Component Tensile Testing per TM1133300 (Appendix 11) for the G1A spline samples using test fixtures T1165900 and T1166201.

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9.14 Dilator to Hub Leak Testing

G1A units (G1A31-G1A60)

Perform the Catheter Leakage Test Method per TM1133400 (Appendix 12) for G1A dilator samples.

10.0 STATISTICAL METHODS

Descriptive statistics (mean, standard deviation, minimum, and maximum), comparative statistics (F-test and T-test) and statistical tolerance limits will be calculated for variable data, as required by the acceptance criteria.

11.0 ACCEPTANCE / REJECTION CRITERIA


Acceptance Criteria are defined in Table 6.1.

12.0 APPENDICIES

- 1 Test Plan
 - 1.1 Test Plan Flow Chart
 - 1.2 Test Implementation Chart
- 2 Data Collection Forms
 - 2.1 Spline & Hook Engagement Integrity
 - 2.2 Post Sterile Dimensional Testing
- 3 Delivery System Simulated Use Test Method (TM1133600, Draft)
- 4 Filter Deployment Force Testing (TM1133100, Draft)
- 5 Post Sterile Dimensional Filter Testing (TM1132600, Draft)
- 6 Radial Strength Testing (TM11327000, Draft)
- 7 Filter Migration Resistance Testing (TM1134800, Draft)
- 8 Recovery Arm Fatigue Testing (TM1133800, Draft)
- 9 Removal Force Testing (TM1132900, Draft)
- 10 Marker Band Security Testing (TM25001164)

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- 11 Delivery System Component Tensile Testing (TM1133300)
- 12 Catheter Leakage Test Method (TM1133400)
- 13 Migration Testing Run Order (Randomized)
- 14 Design Change Summary

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**APPENDIX 12.2: Manufacturing Documentation & Pre-Sterile Raw
Inspection Data**

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APPENDIX 12.3: Raw Test Data Recording Sheets

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APPENDIX 12.4: Statistical Analysis Data Sheets

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APPENDIX 12.5: Failure Investigation Report

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Revision # 12

OML 07

Attachment 1 - Example Only

INVESTIGATOR(S): Madia, vonLinden, Felt	ITEM #: RF-048F Modified (G1A)
DATE: 2-15-05	LOT #: 12-04-038
DESCRIPTION: RNF Filter w/ 0.0105" OD Ground Wire and 40 mm Span	
DESCRIPTION OF FAILURE: Data recording sheet indicates sample #30 failed to meet spec for arm span (35.5 mm vs. 35 mm spec. max.); sample #39 failed to meet spec for leg span (43 mm vs. 42 spec. max.), however QC Inspect worksheet indicates all filters passed inspection.	
PROBABLE ROOT CAUSE: Inspector error in completing QC Inspect worksheet.	
EFFECT ON DEVICE: Impact statement prepared by R&D design team for DV&V report.	
OTHER LOTS TO BE INVESTIGATED: None; appears to be isolated.	
CORRECTIVE ACTION (ON THIS LOT): N/A; lot has been shipped for DV&V testing.	
CONTAINMENT ACTION: N/A; appears to be isolated to this lot.	
PREVENTATIVE ACTION (TO PREVENT RECURRENCE) Review with inspector, stressing importance of Documenting rejects on QC Inspect worksheet.	
VERIFICATION / VALIDATION METHOD USED: (To confirm proposed Preventive Action will not adversely impact the finished device) N/A.	
APPROVAL SIGNATURES	
ENGINEERING: <i>J. Madia</i> 2-16-05	
MANUFACTURING: <i>C. Felt</i> 2/16/05	
QUALITY: <i>Erin Pelt</i> 2-16-05	

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**APPENDIX 12.6: Modified Recovery Filter Respiratory Fatigue Test -
Rationale**

Modified Recovery Filter Respiratory Fatigue Test - Rationale

IVC filters implanted in the Vena Cava are exposed to cyclic stresses caused by normal cardiac and pulmonary functions. While cardiac functions have very low impact on the IVC diameter, pulmonary functions produce a measurable IVC diameter change of about 1mm. These physiological functions cause the IVC to expand and contract resulting in a change of filter geometry. Cyclic stress and the corrosive environment could potentially cause fatigue related fractures. In order to demonstrate the fatigue endurance of the RNF filter, a test was run in which the RNF filter experiences cyclic stresses comparable to 10 years of pulmonary output (or 32 million cycles) in a simulated environment.

Typical fatigue curves for Nitinol are shown in Figures 1¹, 2¹, and 3¹. All curves display a gradual increase in fatigue life with the decrease in stress regardless of the test temperature, heat treatment, or ingot manufacturing methods. Therefore, lower stresses in a Nitinol device should produce longer fatigue life. Also stresses below 200 MPa result in almost an infinite life span as the curves seem to reach the endurance limit.

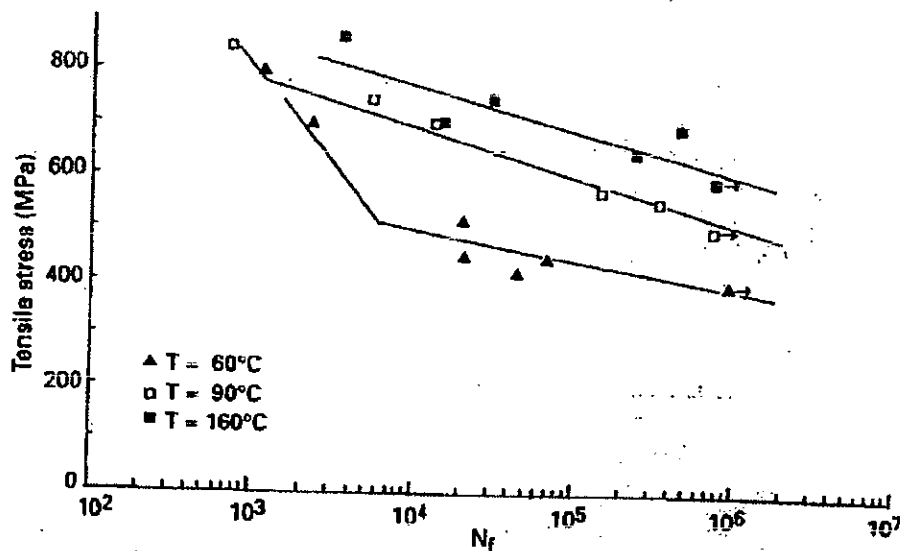


Figure 1. Effect of test temperature on the fatigue life of a Ti-50.8at%Ni alloy, which was annealed at 400 °C for one hour and then cooled in a furnace gradually.

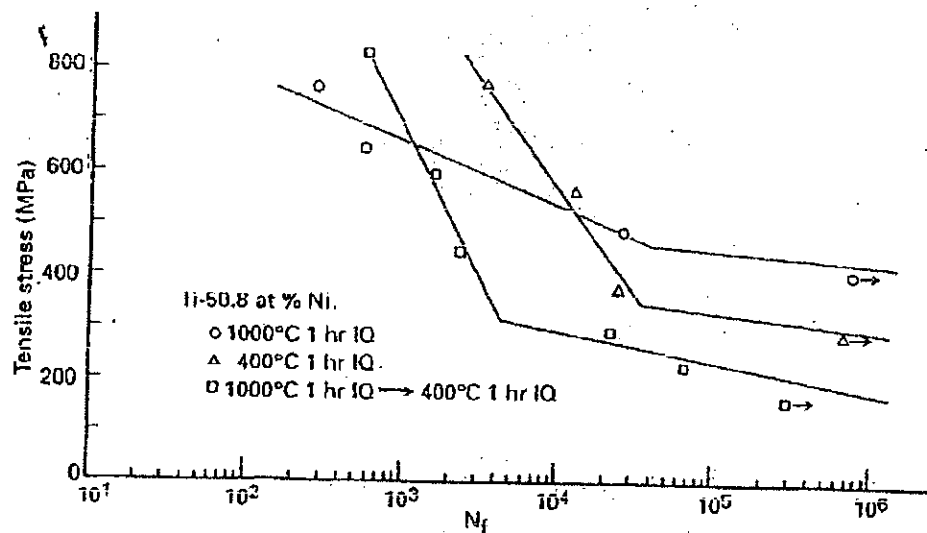


Figure 2. Effect of heat-treatment on the fatigue life of a Ti-50.8at%Ni alloy, which was tested at room temperature.

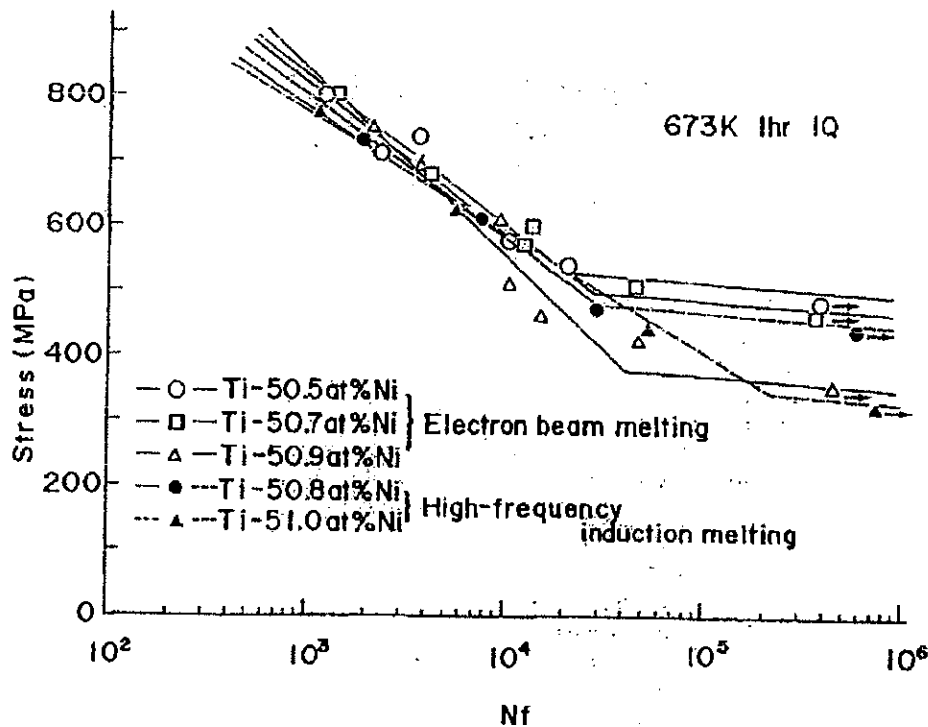


Figure 3. Fatigue lives of Ni-Ti alloys, which were made by electron beam melting and high-frequency vacuum induction melting.

In our test, sixteen (16) filters were subjected to 36 million cycles with 1 mm deflection in an 18.9 mm ID tube. The average ID compliance at all locations was 6.42% with a standard deviation of 0.77. The minimum ID compliance was 5.2%, which is equivalent to 1mm deflection, and the max ID compliance was 7.5% (equivalent to 1.4 mm deflection). The filters were then inspected to ensure that there were no failures; namely cracks, wire deformation, or any sort of physical damage to the filter. The results demonstrate that RNF filters were able to withstand the stress caused by 10 years of simulated pulmonary cycles and maintain integrity.

Peak Stress (MPa)	Original Design			Modified Design		
	Arm	Leg	Hook	Arm	Leg	Hook
Deployed	157.5	94.0	27.5	83.5	82.4	6.9
Peak Strain (%)	Original Design			Modified Design		
	Arm	Leg	Hook	Arm	Leg	Hook
Deployed	1.0	0.40	0.12	0.44	0.36	0.03

Table 1. FEA results for Recovery and G1A filters. The table shows peak strain and stresses in different filter components in the deployed conditions².

The FEA analysis conducted on the original Recovery design and the modified filter (G1A) show that G1A is subjected to much lower stresses in the deployed configuration comparing to the original filter. In particular all sections of the modified filter are under lower stress than their original counterparts. Both filters are subjected to minimal stresses, the highest stress of 157.5 MPa is displayed by the original arm geometry. However, the resulting peak deformation of 1.0% is well within the Nitinol elastic range (typically 7 to 10%)³. Based on the peak stress level values, both the original and modified filters will withstand 32 million cycles (or 10 years equivalent of pulmonary output), however the modified design should exceed the fatigue life of the original Recovery filter thereby eliminating the need for conducting respiratory fatigue test on the modified filter.

REFERENCES

1. Miyazaki, S. (1990). Engineering Aspects of Shape Memory Alloys. London:Butterworth-Heinemann.
2. ETR-05-02-02, Effects of Changes to the Recovery Filter and the Femoral Delivery System on Filter Stresses in Both Loaded and Deployed Conditions based on FEA Analysis.
3. Wayman C.M., Duerig T. W. (1990). Engineering Aspects of Shape Memory Alloys. London:Butterworth-Heinemann.



**ETR-05-02-05
REV 0**

**G1A Recovery Filter Femoral System
Design Verification and Validation Report**

Project # 8027

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1.0 OBJECTIVE / PURPOSE OF TEST

The objective of this study was to verify and validate the design of the G1A Recovery Filter Femoral System (RF-210F), project # 8027. Design verification testing consisted of the following: dimensional, tensile, leak, marker band security, migration resistance, removal force, fatigue, and radial strength testing. Design validation testing consisted of evaluating the performance of the entire system, utilizing a simulated use anatomical model (ref. ETR-05-01-07). A chronic (TPR-04-09-11) and acute (ETR-05-01-06) animal study were also performed as part of design validation.

NOTE: Simulated Use testing consists of the following elements: Trackability, Pushability, Flex/Kink, Filter Advancement, Deployment Force, Deployment Accuracy, Filter Fixation, Ability to Deploy, and Deployment Configuration.

2.0 INTRODUCTION / BACKGROUND


The Recovery Filter is a blood clot trapping device designed to prevent pulmonary embolism by mechanical filtration. The filter is implanted percutaneously in the inferior vena cava (IVC). The Recovery Filter has the additional feature of being able to be percutaneously removed after implantation with minimal trauma to the IVC. The Recovery Filter may be used as a permanent filter or be implanted temporarily to treat a temporary risk of pulmonary embolism.

The G1A Recovery Filter (RF-210F) has been modified, in comparison to the current Recovery Filter (RF-048F), to increase migration and fracture resistance, and to minimize the likelihood of leg twisting, appendage snagging, filter tilting, and caval perforation. These changes include an increased ground wire diameter of the hook from 0.0085" to 0.0105" in order to improve the fracture resistance of the hook and to improve the migration resistance of the filter. The leg span has been increased from 32mm to 40mm in order to improve the ability of the filter to expand with a distending vena cava. The total filter arm length has increased from 20mm to 25mm, enlarging the filter arm span from 30mm to 33mm to aid in filter centering. An additional inward bend has been applied to the end of the filter arm in order to improve arm interaction with the vessel wall, to address caval perforations and appendage snagging. The arc of filter arm, as it attaches to the sleeve, has been modified to have a smooth radiused transition instead of sharp angle. This change was made in order to reduce the stress concentration generated by the sharp angle and thus improve fracture resistance in the area of the filter.

Currently, the Recovery Filter (RF-048F) is deployed via a femoral vein approach using a delivery sheath with the filter mounted on a pusher wire. The new delivery system has been modified to increase the delivery sheath distal tip ID (including the distal marker band) from 0.083 +/- 0.001" to 0.085 +/- 0.002" to allow for ease of delivery of the G1A filter. In addition to the change in sheath tip ID, the OD of the dilator shaft was increased from .079" to .081" to ensure a smooth transition in profile during sheath advancement into the anatomy. Additionally, the mounting spline of the pusher wire has been modified to accommodate the stronger hooks and assist the G1A filter deployment.

The G1A Recovery Filter Femoral System (catalog # RF-210F) consists of a dilator, a 7 French I.D. introducer sheath, and a delivery catheter. The G1A Recovery Filter is preloaded within the storage tube of the delivery system, which consists of pusher pad and spline attached to a

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pusher wire and handle. The Femoral System is packaged in kits. Kit A consists of a dilator and a 7 French introducer sheath. Kit B consists of the delivery system containing the filter placed within a shipping tray. Each Kit is packaged in a separate unit pouch. Both unit pouches are packaged in a final unit pouch.

3.0 REFERENCE DOCUMENTS

- 3.1 TPR-05-01-13: G1A Recovery Filter Femoral System Design Verification and Validation Protocol
- 3.2 TPR-04-09-11: Chronic Animal Study Protocol
- 3.3 ETR-05-02-11: Chronic Animal Study Report *(test report pending)*
- 3.4 ETR-05-01-07: Validation of the Farlow Scientific Inc. Venous Anatomical Model
- 3.5 ETR-05-01-08: G1A Recovery Filter Femoral System Feasibility Test Report
- 3.6 ETR-05-01-06: G1A Recovery Filter Femoral System Acute Animal Study Report
- 3.7 ETR-04-12-15: G1A Recovery Filter Feasibility with Jugular/Subclavian System
- 3.8 ETR-04-10-04: G1A Recovery Filter (0.0105" x 0.060") Feasibility Phase 1
- 3.9 ETR-04-10-21: Removable G1A Filter, (Preliminary) Acute Animal Study
- 3.10 ETR-04-08-04: Recovery Filter (RF) Arm Fatigue Test Report (Feasibility Study)
- 3.11 ETR-04-06-06: Recovery Filter (RF) Migration Resistance Improvement DOE and Hook Radius Change (Feasibility Study)
- 3.12 TM1133300: Delivery System Component Tensile Test Method
- 3.13 TM1133400: Catheter Leakage Test Method
- 3.14 TM1133100: Vena Cava Filter Deployment Force Test Method
- 3.15 TM1133600: Delivery System Simulated Use Test Method
- 3.16 TM1134800: Migration Resistance
- 3.17 TM1135200: Filter Deployment Force Test
- 3.18 TM1132600: Post Sterile Dimensional Filter Testing
- 3.19 TM1132700: IVC Filter Radial Force Method
- 3.20 TM1134800: Filter Migration Resistance Testing
- 3.21 TM1133800: Recovery Filter Arm Fatigue Test
- 3.22 TM1132900: Recovery Filter Removal Force Test Method
- 3.23 TM1133300: Delivery System Component Tensile Testing
- 3.24 TM1133400: Catheter Leakage Test Method
- 3.25 TM1132600: Filter Dimensional Test
- 3.26 TM25001164: Band/Immobile Tensile Test *(GFO Test Method)*
- 3.27 RNF Fact Book #7081, Volume 1 of 13, Section 3, p 3 of 4
- 3.28 R5530435 BOM/Routing Process Report *(Preliminary DMR)*
- 3.29 RA070025: Risk Assessment of the G1A Recovery Filter Femoral System
- 3.30 DFMEA070022: Design Failure Mode and Effects Analysis of the G1A Recovery Filter Femoral System
- 3.31 PPS070028: G1A Recovery Filter Femoral System PPS

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4.0 TEST PROCEDURE

All samples were sent to Covington, GA for 2x EO (cycle 7) sterilization.

Thereafter, all samples were environmentally stressed using the following procedures outlined in TM0635 (Covington document).

- Performed accelerated age testing at 62.8 °C for 24 hours per section 6.2 in TM0635.
- Performed environmental stress conditioning for 24 hours per section 6.3.3 in TM0635.
- Allowed product to stabilize at room temperature for 24 hours (not outlined in TM0635).
- Performed ship testing on all samples per TM0358.

Reference Appendix 12.1 for the DV&V Protocol that displays the test procedure details and order of testing.

5.0 TEST MATERIALS

Test units were from the following lots:

- G1A total units 136
 - 35 units from Lot 01-05-024
 - 33 units from Lot 01-05-025
 - 35 units from Lot 01-05-026
 - 33 units from Lot 01-05-027
- SNF total units 119
 - 30 units from Lot GFOL3376
 - 90 units from Lot GFOL3377
 - 20 units from Lot GFOL0112
- RNF total units 60
 - 40 units from Lot GFOL2722
 - 20 units from Lot GFOJ0984

6.0 DEVIATIONS / EXCEPTIONS TO TEST PROTOCOL

- 6.1 The data for some test results were found to be non-normally distributed. These results were treated as attribute data or further evaluated using Weibull Regression Analysis. Details of the data analysis for each test are found in section 7.0 Test Results.
- 6.3 Migration Resistance @ 32mm - There was only one data point obtained for the SNF 32mm migration resistance when testing the first 30 filters. An additional 9 SNF filters were tested from a new lot of filters to achieve a total of 5 data points for 32mm SNF migration resistance. The 9 additional units were from a lot that was exposed to only one sterilization cycle. Therefore, these 9 units deviate from the specified 2x EtO, ship simulation and storage thermal cycle simulation. Additional RNF units were tested for migration in the 32mm simulated IVC for comparative analysis. These RNF units were not specified in the protocol. The additional RNF and SNF units were tested with clots

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made from the large ID sausage casing, whereas the initial filters were tested with clots made from the small ID sausage casing.

- 6.4 The post sterile distal and proximal marker band OD measurements were specified in the protocol to be analyzed separately as variable data. Due to the similarities in the device design, non-normality of the data, sample sizes and the same specification, the post sterile distal and proximal marker band OD measurements were pooled and used as attribute data.
- 6.5 The pre-sterile spline OD measurements were specified in the protocol to be analyzed as variable data. Due to the non-normality of the data and sample sizes, the pre-sterile spline OD measurements could not be analyzed as variable data. The spline is made of stainless steel and is unchanged by the sterilization cycle. Therefore, an additional 60 spline OD measurements were taken post sterile and used as attribute data in place of the pre-sterile data.
- 6.6 One pair of filter arms from Lot#12-04-038 was found to have an arm span dimension of 35.5mm during the manufacturing pre-sterile inspection. This single data point exceeds the specification (maximum of 35mm). The filter was not scrapped by the operator as specified in the inspection procedure IPG625 and was included as one of the samples used in the DV&V testing. The Failure Investigation Report (see Appendix 12.5) found the root cause of this failure to scrap the filter to be operator error. The corrective action taken was re-training the operator stressing the importance of documenting and scrapping rejects.

The out of specification filter was not marked or labeled. It is uncertain as to the DV&V testing for which this filter was used. Therefore, the effect of a filter with one pair of arms that is .5mm over the specification was considered for the following tests:

- Bench Deployment Simulated Testing – Filter deployment configuration and filter centering may be affected by an out of specification arm span.
- Deployment Force Testing – The force required to deploy the filter, filter deployment configuration and filter centering may be affected by an out of specification arm span.
- Post Deployment Arm Span Dimension - The dimension of the filter after deployment may be affected by an out of specification arm span.
- Migration Resistance Testing – The ability of the filter to resist migration may be affected by an out of specification arm span.
- Filter Removal Force Testing - The force to remove the filter may be affected by an out of specification arm span.

There were no outliers found in the testing described above. Therefore, it is concluded that this deviation had no effect on the test data.

- 6.7 One pair of filter legs from Lot#12-04-038 was found to have a leg span dimension of 43.0mm during the manufacturing pre-sterile inspection. This exceeds the specification maximum of 42.0mm. The filter was not scrapped by the operator as specified in the inspection procedure IPG625, and was included as one of the samples used in the DV&V testing. The Failure Investigation Report (see Appendix 12.5) found the root cause of this failure to scrap the filter to be operator error. The corrective action taken

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was re-training the operator stressing the importance of documenting and scrapping rejects.

The out of specification filter was not marked or labeled. It is uncertain as to the DV&V testing for which this filter was used. Therefore, the effect of a filter with one pair of legs that is 1mm over the specification was considered for the following tests:

- Bench Deployment Simulated Testing – Filter deployment configuration and filter centering may be affected by an out of specification leg span.
- Deployment Force Testing – The force required to deploy the filter, filter deployment configuration and filter centering may be affected by an out of specification leg span.
- Post Deployment Leg Span Dimension - The dimension of the filter after deployment may be affected by an out of specification leg span.
- Filter Leg Radial Strength Testing – The radial force of the filter may be affected by an out of specification leg span.
- Migration Resistance Testing – The ability of the filter to resist migration may be affected by an out of specification leg span.
- Filter Removal Force Testing - The force to remove the filter may be affected by an out of specification leg span.

There were no outliers found in the testing described above. Therefore, it is concluded that this deviation had no effect on the test data.

- 6.8 The rating scale of 1-4 for simulated use testing as specified in the protocol was in reverse order from the rating scale of TM1133600. The rating scale defined in the protocol was used for the testing. All units tested were rated as acceptable or better.
- 6.9 The distal marker band OD, proximal marker band OD and dilator OD measurements were taken from units 1-30 instead of units 61-90 as specified by the protocol. This deviation was made in order to test efficiently by measuring the units that were available at the time. There were no anticipated differences in units 1-30 and 61-90 for these dimensions.
- 6.10 The G1A units for this study were specified in the protocol to be representative of the commercial product. The G1A units for this study were not packaged with an IFU as will be the commercial product. However, the packaging for this product is the same as that of the RNF. The RNF has successfully completed a packaging validation that provided evidence that the product was protected from damage and remained sterile after 2x EtO, ship simulation and storage thermal cycle simulation. Therefore, it is concluded that this deviation had no effect on the test data.

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7.0 TEST RESULTS / SUMMARY OF DATA

NOTE: Raw data, summary statistics and normality testing can be found in the appendices (12.2 through 12.4).

7.1 Pre-Sterile Dimensional/Visual Inspection Test Results

*Table 1. Pre-Sterile Dimensions measured at Glens Falls
(Normal Data evaluated as Variable)*

Component	Qty. Measured	Qty. Scraped	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	LSL 95/95	USL 95/95	Result
Dilator OD (in)	53	0	0.081	0.0006	0.079	0.082	0.081 + .002 - .002	0.079	0.082	Pass

NOTE: The sample population was normal ($p\text{-value} \geq 0.05$) based on the Shapiro-Wilks W statistic at the 95% confidence level.

*Table 2. Pre-Sterile Dimensions measured at Glens Falls
(Non-Normal Data evaluated as Attribute)*

Component	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	Result
Filter Arm Span (mm)	438	34	0.7	30	35	30-35	Pass
Filter Leg Span (mm)	438	41	0.5	39	42	38-42	Pass
Ground Wire OD (in)	100	0.0105	0.0001	0.0103	0.0107	0.0105 + .0005 - .0005	Pass
Filter Arm Length (mm)	876	18.62	0.310	17.78	19.57	18.75 +1.00 -1.00	Pass
Swaged Distal Marker OD (in)	140	0.120	0.0004	0.118	0.120	0.118 + .002 - .002	Pass
Swaged Proximal Marker OD (in)	140	0.120	0.0002	0.119	0.120	0.118 + .002 - .002	Pass

NOTE: The sample populations in Table 2 were non-normal ($p\text{-value} \leq 0.05$) based on the Shapiro-Wilks W statistic at the 95% confidence level. Therefore, the results were treated as attribute data. The individual measurements met the 95% confidence and 95% reliability attribute specification of 59 samples minimum with no failures.

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*Table 3. Pre-Sterile Dimensions measured at Glens Falls
(Non-Normal Data evaluated as Attribute)*

Component	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	Result
Pre-Sterile Spline OD (in)	33	0.081	0.0005	0.080	0.081	0.081 +.001 -.001	Insufficient Sample Size*
Post Sterile Spline OD Over Slotted Area (in)	60	0.080	0.0005	0.080	0.081	0.081 +.001 -.001	Pass
Post Sterile Spline OD At Stop Area (in)	60	0.081	0.0003	0.080	0.081	0.081 +.001 -.001	Pass

NOTE*: The sample population for pre-sterile spline OD was non-normal (p-value ≤ 0.05) based on the Shapiro-Wilks W statistic at the 95% confidence level. There were an insufficient number of samples to evaluate the pre-sterile OD data as attribute data (95/95). Therefore, an additional 60 OD measurements were taken for both ends of the spline. These were taken post sterile and used as attribute data in place of the pre-sterile data. All individual measurements met the 95% confidence and 95% reliability attribute specification of 59 samples minimum with no failures. (See deviation section 6.5 for further details)

*Table 4. Pre-Sterile Dimensional/Visual Test Results performed at Glens Falls
(Attribute Data)*

Component	Qty Measured	Qty Scrapped	Acceptance Criteria	Result (Post-Scrap)
Hook Dimensions	900	1	Must meet visual inspection Template TA-6004-1024.	Pass
Introducer Sheath Tip ID	200	0	Sheath Tip must accept a 0.084" OD plus pin gage.	Pass
Swaged Distal Marker ID (0.083" Pin Must Fit)	70	0	Sheath Tip must accept a 0.083" OD minus pin gage.	Pass
Swaged Proximal Marker ID (0.083" Pin Must Fit)	70	1	Sheath Tip must accept a 0.083" OD minus pin gage.	Pass

NOTE: The units were measured during manufacturing at Glens Falls. Out of specification units were scrapped according to the manufacturing procedures.

7.2 Post-Sterile Dimensional/Visual Inspection Test Results

Table 5. Post-Sterile Dimensional Test Results (Reference Data)

Component	Qty. (n)	Mean	Std. Dev.	Min.	Max.
Filter Arm Span (mm) For Information Only	90	33	0.4	31	33
Filter Leg Span (mm) For Information Only	90	40	0.4	39	41

NOTE: This data was taken for informational purposes only. Therefore, there is no pass or fail criteria.

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*Table 6. Post-Sterile Dimensional Test Results
(Non-Normal Data Pooled and evaluated as Attribute)*

Component	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	Result
Swaged Distal Marker OD (in)	30	0.120	0.0005	0.118	0.120	0.118 +.002 -.002	Insufficient sample size*
Swaged Proximal Marker OD (in)	30	0.120	0.0005	0.119	0.120	0.118 +.002 -.002	Insufficient sample size*
Pooled Swaged Distal & Proximal Marker OD (in)	60	0.120	0.0005	0.118	0.120	0.118 +.002 -.002	Pass

NOTE*: The sample populations for swaged distal and proximal marker OD were non-normal (p-value ≤ 0.05) based on the Shapiro-Wilks W statistic at the 95% confidence level. The distal and proximal marker band components are the same. The dimensions (ID/OD) of the sheath and mandrel over which the distal and proximal marker bands are swaged are also the same. Therefore, the results were pooled into one data set and treated as attribute data. The individual measurements met the 95% confidence and 95% reliability attribute specification of 59 samples minimum with no failures. (See deviation section 6.4 for further details)

*Table 7. Post-Sterile Dimensional Test Results
(Non-Normal Data evaluated using Weibull Analysis)*

Component	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	LSL 95/95	USL 95/95	Result
Dilator OD (in)	30	0.081	0.0007	0.080	0.082	0.081 +.002 -.002	0.080	0.082	Pass*

NOTE*: The Dilator OD sample population was non-normal (p-value ≤ 0.05) based on the Shapiro-Wilks W statistic at the 95% confidence level. The sample size of 30 measurements was insufficient to perform a Chi-Square Test. Therefore, the USL and LSL at 95% confidence and 95% reliability were calculated using a Weibull Analysis.

*Table 8. Post-Sterile Dimensional/Visual Test Results
(Attribute Data)*

Component	Qty. (n)	Acceptance Criteria	Result
Introducer Sheath Tip ID	60	Sheath Tip must accept a 0.065" OD min pin gage.	Pass
Swaged Distal Marker ID	60	Sheath Tip must accept a 0.083" OD minus pin gage.	Pass
Swaged Proximal Marker ID	60	Sheath Tip must accept a 0.083" OD minus pin gage.	Pass
Dilator ID	60	Sheath Tip must accept a 0.038" OD plus pin gage.	Pass
Spline/Filter Interaction	136	Filter hooks must not dislodge from spline during shipping or handling.	Pass

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7.3 Bench Top Simulated Use Test Results

Rating Scale:

4 = Excellent/Exceptional

3 = Good

2 = Acceptable

1 = Unacceptable

*Table 9. Bench Top Simulated Use Test Results
(Attribute Data)*

Performance Requirement	Qty. (n)	PPS Specification	Acceptance Criteria	Result
Kink Resistance Sheath/Introducer	120	Sheath and introducer must resist kinking and crushing.	Pass/Fail	Pass
Dilator Removal	120	The dilator must be able to be removed safely with minimal force.	Pass/Fail	Pass
Filter Compression Profile	120	The filter is deliverable through a 7 Fr ID introducer sheath.	Pass/Fail	Pass
Filter Advancement	120	The user must be able to advance the filter through the delivery system with a force rated acceptable.	Rating ≥ 2	Pass
Kink Resistance Pusher Rod	120	The pusher rod must resist kinking and crushing.	Pass/Fail	Pass
Filter Deployment Accuracy	60	The user must be able to accurately deploy the filter.	(± 10 mm of intended target)	Pass
Filter Centering	120	The filter sleeve must be at a minimum distancing of 1/3 the radius from the vessel wall.	Pass/Fail	Pass
Deployment Configuration	120	The filter must deploy with no arm or leg entanglement.	Pass/Fail	Pass

7.4 Deployment Force Test Results

*Table 10. Delivery Peak Force Test Results
(Non-Normal Data evaluated as Attribute)*

Performance Requirement	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	Result
Delivery Peak Force (lbf)	60	3.73	0.517	1.82	4.98	≤ 5	Pass

NOTE: The delivery peak force sample population in was non-normal (p-value ≤ 0.05) based on the Shapiro-Wilks W statistic at the 95% confidence level. Therefore, the delivery peak force measurements were treated as attribute data. The individual measurements met the 95% confidence and 95% reliability attribute specification of 59 samples minimum with no failures.

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7.5 Filter Leg Radial Strength

Table 11. Filter Leg Radial Strength Test Results
(Non-Normal Data evaluated using W-Test Comparison of Medians at 95% Confidence)

Filter Type	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	p-value	Result
G1A Radial Force (grams)	30	4.5	0.23	3.6	4.8	G1A ≤ SNF	2.78E-11	Pass
SNF Radial Force (grams)	30	10.9	2.72	5.9	19.0			

NOTE: The sample populations were non-normal (p-value < 0.05) based on the Shapiro-Wilks test at the 95% confidence level. Therefore, Mann-Whitney W-Test was performed to compare medians at 95 % confidence level. The resulting p-value was below .05. Therefore, there is a statistically significant difference between the medians. The median of the SNF was greater than that of the G1A. Therefore, the result is a pass of the acceptance criteria.

7.6 Filter Removal Force

Table 12. Removal Peak Force Test Results
(Non-Normal Data evaluated using Weibull Analysis)

Performance Requirement	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	USL 95/95	Result
Removal Peak Force (lbf)	30	3.37	0.336	2.92	4.29	< 5	4.05	Pass


NOTE: The removal peak force sample population was non-normal (p-value ≤ 0.05) based on the Shapiro-Wilks W statistic at the 95% confidence level. The sample size of 30 measurements was insufficient to perform a Chi-Square Test. Therefore, the USL at 95% confidence and 95% reliability was calculated using a Weibull Analysis.

7.7 Marker Band Security Test Results

Table 13. Marker Band Security Test Results
(Attribute Data)

Component	Qty. (n)	Number of Bands that Moved	Acceptance Criteria	Result
Marker Band on Introducer Sheath	30	0	No movement	Pass

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7.8 Tensile Strength Test Results

*Table 14. Tensile Test Results & Capability Assessment
(Non-Normal Data evaluated using Weibull Analysis)*

Joint or Component	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	LSL 95/95	Result
Dilator to Hub Joint (lbf)	30	11	1.1	8	12	≥ 5	8	Pass*
Spline to Wire Joint (lbf)	30	41	13.1	24	62	≥ 5	20	Pass*

NOTE*: The both sample populations were non-normal ($p\text{-value} \leq 0.05$) based on the Shapiro-Wilks W statistic at the 95% confidence level. The sample sizes of 30 measurements were insufficient to perform a Chi-Square Test. Therefore, the LSL at 95% confidence and 95% reliability were calculated using a Weibull Analysis.

7.9 Leakage Test Results

*Table 15. Leakage Test Results
(Attribute Data)*

Joint or Component	Qty. (n)	No. of Leaks	Acceptance Criteria	Result
Dilator to Hub Joint	30	0	No leak	Pass

7.10 Filter Migration Test Results

7.10.1 15mm and 28mm Minimum Migration Resistance Pressure

*Table 16. Combined 15mm & 28mm Filter Migration Resistance Test Results
(Attribute Data)*

Filter Type	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	Result
G1A - 15mm Cava (mmHg)	30	150 *	N/A	150 *	150 *	≥ 50	Pass
G1A - 28mm Cava (mmHg)	30	106.3	19.36	81.6	150 *	≥ 50	Pass
Combined G1A - 15mm Cava G1A - 28mm Cava (mmHg)	60	N/A	N/A	81.6	150 *	≥ 50	Pass

NOTE*: The migration test equipment has an upper limit of 150mmHg. Therefore, the testing was stopped upon filters reaching 150 mmHg.

7.10.2 15mm IVC Migration Resistance Pressure

*Table 17. 15mm Filter Migration Resistance Comparison of Variance
(Non-Normal Data evaluated as Attribute)*

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Filter Type	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	p-value	Result
SNF - 15mm Cava (mmHg)	30	150	N/A	150	150	G1A filter must have equivalent or less variation as SNF	N/A	Pass
G1A - 15mm Cava (mmHg)	30	150	N/A	150	150			

NOTE: The migration test equipment has an upper limit of 150mmHg. Therefore, the testing was stopped upon filters reaching 150 mmHg. All filters reached the maximum value of 150 mmHg. Therefore, the F-test for migration results of the G1A and SNF could not be calculated but were deemed acceptable in a 15mm simulated IVC.

*Table 18. 15mm Filter Migration Resistance Comparison of Central Tendency
(Non-Normal Data evaluated as Attribute)*

Filter Type	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	p-value	Result
SNF - 15mm Cava (mmHg)	30	150	N/A	150	150	G1A filter must be statistically equivalent or greater than SNF	N/A	Pass
G1A - 15mm Cava (mmHg)	30	150	N/A	150	150			

NOTE: The migration test equipment has an upper limit of 150mmHg. Therefore, the testing was stopped upon filters reaching 150 mmHg. All filters reached the maximum value of 150 mmHg. Therefore, the T-test for migration results of the G1A and SNF could not be calculated but were deemed acceptable in a 15mm simulated IVC.

7.10.3 28mm IVC

A number of SNF, G1A and RNF filters did not migrate (n=7, 11, and 4 respectively) due to clots passing the filters and therefore, inability to occlude the cava sufficiently. These data points were not included in the analysis. Additional filters were tested to produce total of 30 migration data points for each implant.

Table 19. 28mm Filter Migration Resistance Summary of Test Results (mmHg)

Filter Type	Number of Runs (n)	Mean	Std. Dev.	Min.	Max.
SNF	30	121.6	24.02	56.7	150
G1A	30	106.3	19.36	81.6	150
RNF	30	56.5	11.05	27.3	73.1

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*Table 20. 28mm Filter Migration Resistance Comparison of Variance
(Non-Normal Data evaluated comparatively using Standard Deviations)*

Filter Type	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	p-value	Result
SNF - 28mm Cava (mmHg)	30	121.6	24.02	56.7	150 *	G1A filter must have equivalent or less variation as SNF	N/A	Pass
G1A - 28mm Cava (mmHg)	30	106.3	19.36	81.6	150 *			

NOTE*: The migration test equipment has an upper limit of 150mmHg. Therefore, the testing was stopped upon filters reaching 150 mmHg. Some filters reached the maximum value of 150 mmHg. These data points were included in the statistical analysis even though they are truncated data. The data for SNF and G1A were found to be non-normal. Therefore, the F-test for migration results of the G1A and SNF could not be calculated. However, the standard deviation of the G1A filter was less than that of the SNF in a 28mm simulated IVC.

*Table 21. 28mm Filter Migration Resistance Comparison of Central Tendency
(Non-Normal Data evaluated using Mann-Whitney W-test of Medians)*

Filter Type	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	p-value	Result
SNF - 28mm Cava (mmHg)	30	121.6	24.02	56.7	150 *	G1A filter must be statistically equivalent or greater than SNF	.0046	Fail
G1A - 28mm Cava (mmHg)	30	106.3	19.36	81.6	150 *			

NOTE*: The migration test equipment has an upper limit of 150mmHg. These data points were included in the statistical analysis even though they are truncated data. The data for SNF and G1A were found to be non-normal (p-value < 0.05) based on the Shapiro-Wilks W statistics at the 95% confidence level. The T-test for migration results of the G1A and SNF could not be calculated. Therefore, the Mann-Whitney W-test was performed to compare medians at the 95% confidence level. The resulting p-value was less than .05. Therefore, there is a statistically significant difference between the medians. The median of the SNF was greater than that of the G1A. Therefore, the result is a failure of the acceptance criteria.

*Table 22. 28mm Filter Migration Resistance Comparison of Central Tendency
(Non-Normal Data evaluated using Mann-Whitney W-test of Medians)*

Filter Type	Qty. (n)	Mean	Std. Dev.	Min.	Max.	p-value	Result
RNF - 28mm Cava (mmHg)	30	56.5	11.05	27.3	73.1	3.02E-11	G1A filter is statistically greater than RNF
G1A - 28mm Cava (mmHg)	30	106.3	19.36	81.6	150 *		

NOTE*: The migration test equipment has an upper limit of 150mmHg. Therefore, the testing was stopped upon filters reaching 150 mmHg. Some filters reached the maximum value of 150 mmHg. These data points were included in the statistical analysis even though they are truncated data. The data for RNF and G1A were found to be non-normal (p-value < 0.05) based on the Shapiro-Wilks W statistics at the 95% confidence level. The T-test for migration results of the G1A and RNF could not be calculated. Therefore, the Mann-Whitney W-test was performed to compare medians at the 95% confidence level. The resulting p-value was less than .05. Therefore, there is a statistically significant difference between the medians. The median of the G1A was greater than that of the RNF. Therefore, the result is a pass of the acceptance criteria.

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7.10.4 32mm IVC

A number of SNF, G1A and RNF filters did not migrate (n=32, 26, and 2 respectively) due to clots passing the filters and therefore, inability to occlude the cava sufficiently. Additional filters were tested to produce total of 5 migration data points for each implant, so that a statistical comparison could be made.

Table 23. 32mm Filter Migration Resistance Summary of Test Results (mmHg)

Filter Type	Number of Runs (n)	Mean	Std. Dev.	Min.	Max.
SNF	5	70.4	13.0	55.8	91.4
G1A	5	73.2	3.0	69.9	76.6
RNF	5	35.2	2.2	32.1	37.7

Table 24. 32mm Filter Migration Resistance Comparison of Central Tendency (Normal Data)

Filter Type	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	p-value	Result
SNF - 32mm Cava (mmHg)	5	70.4	13.0	55.8	91.4	G1A filter must be statistically equivalent or greater than SNF	.651	Pass
G1A - 32mm Cava (mmHg)	5	73.2	3.0	69.9	76.6			

NOTE: The data for SNF and G1A were found to be normal (p-value > 0.05) based on the Shapiro-Wilks W statistics at the 95% confidence level. The T-test (unequal variance) for migration results of the G1A and SNF resulted in a p-value greater than .05. Therefore, there is not a statistically significant difference between the two means. The mean of the G1A was greater than that of the RNF. Therefore, the result is a pass of the acceptance criteria.

Table 25. 32mm Filter Migration Resistance Comparison of Central Tendency (Normal Data)

Filter Type	Qty. (n)	Mean	Std. Dev.	Min.	Max.	p-value	Result
RNF - 32mm Cava (mmHg)	5	35.2	2.2	32.1	37.7	1.52E-8	G1A filter is statistically greater than RNF
G1A - 32mm Cava (mmHg)	5	73.2	3.0	69.9	76.6		

NOTE: The data for RNF and G1A were found to be normal (p-value > 0.05) based on the Shapiro-Wilks W statistics at the 95% confidence level. The T-test (equal variance) for migration results of the G1A and RNF resulted in a p-value less than .05. Therefore, there is a statistically significant difference between the two means. The mean of the G1A was greater than that of the RNF. Therefore, the result is a pass of the acceptance criteria.

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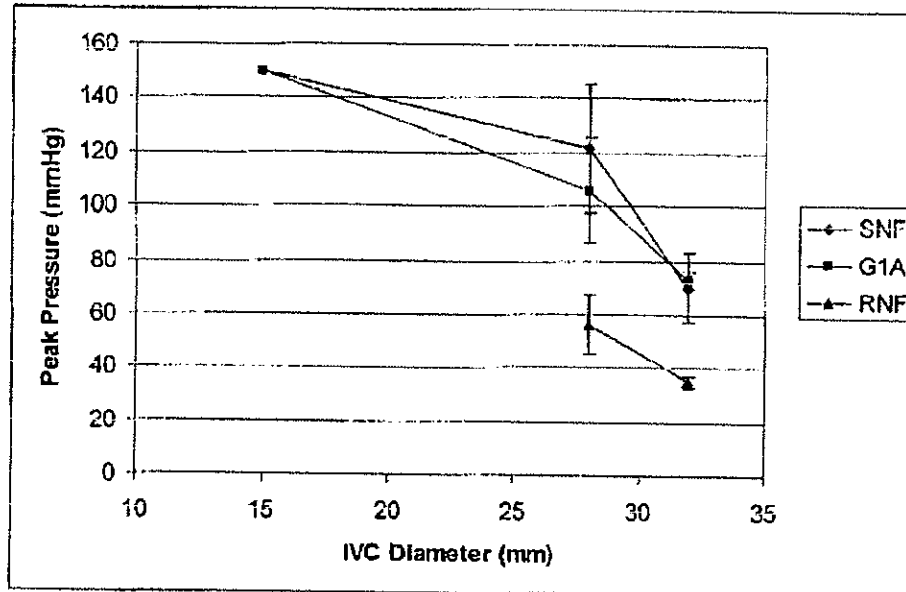


Figure 1. Filter Migration Resistance Summary.

7.11 Filter Arm Cyclic Fatigue Test Results

Table 27. Filter Arm Cyclic Fatigue Test Results (# Cycles to Failure)

Filter Type	Number of Samples (n)	Mean	Std. Dev.	Min.	Max.
RNF	30	51	13.6	29	90
G1A	30	606	106.5	350	850


NOTE: G1A sample population was normal (p -value > 0.05) and RNF sample population was non-normal (p -value ≤ 0.05) based on the Shapiro-Wilks W statistic at the 95% confidence level.

Table 28. Filter Arm Cyclic Fatigue Comparison of Central Tendency (Non-Normal Data evaluated using Mann-Whitney W-test of Medians)

Filter Type	Qty. (n)	Mean	Std. Dev.	Min.	Max.	Accept. Criteria	p-value	Result
RNF	30	51	13.6	29	90	G1A filter must be statistically greater than RNF	0.000	Pass
G1A	30	606	106.5	350	850			

NOTE*: The data for RNF was found to be non-normal (p -value < 0.05) based on the Shapiro-Wilks W statistics at the 95% confidence level. The T-test for fatigue results of the G1A and RNF could not be calculated. Therefore, the Mann-Whitney W-test was performed to compare medians at the 95% confidence level. The resulting p -value was less than .05. Therefore, there is a statistically significant difference between the medians. The median of the G1A was greater than that of the RNF. Therefore, the result is a pass of the acceptance criteria.

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8.0 ANALYSIS OF DATA

Statistical analyses were performed using STATGRAPHICS *Plus*. Data sets were analyzed for normality using the following criteria. The Shapiro-Wilks *W* statistic at the 95% confidence level compared the quartiles of the fitted normal distribution to the quantiles of the data. The standardized skewness test evaluated lack of symmetry in the data. The standardized kurtosis test evaluated whether the distributional shape is either flatter or more peaked than the normal distribution.

Data found to be non-normally distributed by the Shapiro-Wilks *W* test was analyzed as attribute data when sufficient sample sizes were available. In the event of insufficient samples sizes to meet the minimum attribute sampling requirement, the data was analyzed for normality using the Chi-Square Test. Data found non-normal by the Chi-Square Test was evaluated using Weibull Regression Analysis. The Weibull analysis was used to calculate the 95% confidence and 95% reliability specification limits.

When comparative data sets were found to be non-normally distributed, a Mann-Whitney *W* test was used to compare the medians of the two samples. This was accomplished by combining the two samples, sorting the data from smallest to largest, and comparing the average ranks of the two samples in the combined data.

9.0 DISCUSSION OF RESULTS

The following acceptance criteria were met:


9.1 Pre-Sterile Dimensional/Visual Inspection Test Results

- Dilator ID
- Filter Arm Span
- Filter Leg Span
- Ground Wire OD
- Filter Arm Length
- Swaged Distal Marker OD
- Swaged Proximal Marker OD
- Spline OD
- Hook Dimensions
- Introducer Sheath Tip ID
- Swaged Distal Marker ID
- Swaged Proximal Marker ID

9.2 Post Sterile Dimensional/Visual Inspection Test Discussion

- Filter Arm and Leg Span
- Swaged Distal/Proximal Marker OD
- Dilator OD
- Introducer Sheath Tip ID
- Swaged Distal Marker ID

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- Swaged Proximal Marker ID
- Dilator ID
- Spline/Filter Interaction

9.3 Bench Top Simulated Use Test Discussion

- Kink Resistance Sheath/Introducer
- Dilator Removal
- Filter Compression Profile
- Filter Advancement
- Kink Resistance Pusher Rod
- Filter Deployment Accuracy
- Filter Centering
- Deployment Configuration

9.4 Delivery Force Test

9.5 Filter Leg Radial Strength Test

9.6 Filter Removal Force Test

9.7 Marker Band Security Test Discussion

9.8 Tensile Strength Test Discussion

9.9 Leakage Test Discussion

9.10 Migration Resistance in 15 mm IVC

- G1A ≥ 50 mmHg

9.11 Migration Resistance in 28 mm IVC

- G1A Variance \leq SNF Variance
- G1A ≥ 50 mmHg

9.12 Migration Resistance in 32 mm IVC

- G1A \geq SNF

9.13 Filter Arm Cyclic Fatigue Test


The following acceptance criteria could not be statistically analyzed:

9.14 Migration Resistance in 15 mm IVC

- G1A \geq SNF:

All G1A and SNF filters reached the maximum value of 150 mmHg that the testing system could produce. Therefore, there is no way to determine statistical equivalency

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between the filters or lack of thereof. The achieved peak pressures were three times higher than the minimum requirement of 50 mmHg based on the PPS. Based on this data we determined that the performance of G1A was equivalent to SNF and G1A was able to withstand minimum of 50 mmHg pressure.

9.15 Migration Resistance in 28 mm IVC

- G1A Variance \leq SNF Variance:

The data for SNF and G1A were found to be non-normal. Therefore, the F-test for migration results of the G1A and SNF could not be calculated. However, the standard deviation of the G1A filter was less than that of the SNF in a 28mm simulated IVC.

The following acceptance criteria were not met:

9.16 Migration Resistance in 28 mm IVC

- G1A \geq SNF

The data produced from this testing did not meet the acceptance criteria, as defined in the protocol/PPS. However, the G1A filter did significantly outperform the current RNF filter in the 28 mm IVC. Specifically, all G1A filters migrated at pressures in excess of 80 mmHg, whereas all RNF filters migrated at pressures below 80 mmHg. Additionally, when compared to previous competitive testing (ref. ETR 04-03-02), the G1A filter performed comparably or better than many of the competitor's filters.


10 CONCLUSION

The G1A Recovery Filter Femoral System met all of the acceptance criteria, as defined in PPS070028 and the protocol (TPR-05-01-13), with the exception of Migration Resistance being greater than or equal to that of the SNF at 28mm. While the G1A Recovery Filter (RF210F) did not meet this criterion, it did show significant improvement over the current Recovery Filter (RF048F). Specifically, all G1A filters migrated at pressures in excess of 80 mmHg, whereas all RNF filters migrated at pressures below 80 mmHg. Also, when compared to previous competitive device migration testing the G1A Recovery Filter performed at a comparable or higher level than most competitors' product. Therefore, the migration resistance acceptance criteria (at 28mm) may have been inappropriately established and in excess of the true goal of the Recovery G1A Fast Track project, which was to significantly improve the migration resistance of the Recovery filter. Taking this factor into consideration, the data presented in this report does support the goal of the project. Therefore, it is recommended that the PPS requirements for migration resistance be adjusted to more accurately match the goal of the project. Having taken this action, the data in this study may be used to support the regulatory submissions and ultimate commercialization of the G1A filter.

11 RECOMMENDATIONS

The G1A Recovery Filter Femoral System demonstrated acceptable performance in all tests except for migration resistance equivalence to SNF at 28mm. The G1A Recovery Filter demonstrated superior performance in migration resistance over the RNF. Therefore, the following changes to the PPS are recommended for the G1A Recovery Filter Femoral System.

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Filter Migration Resistance, Change From:

User Requirement	Engineering Specification
Migration resistance of G1A must be statistically equivalent to or greater than that of the SNF filter.	<p>Migration resistance of G1A in simulated IVC diameters of 15 mm and 28 mm must be statistically equivalent to or greater than that of SNF filter.</p> <p>Standard deviation of G1A results in simulated IVC diameters of 15 mm and 28 mm must be statistically equivalent to or smaller than that of SNF filter.</p> <p>G1A must withstand a minimum of 50 mmHg pressure in simulated IVC diameters of 15 mm and 28 mm.</p>

Filter Migration Resistance, Change To:

User Requirement	Engineering Specification
Migration resistance of G1A must be statistically greater than that of the RNF filter in a 28mm diameter simulated IVC.	<p>Migration resistance of G1A in a simulated IVC diameter of 28 mm must be statistically greater than that of RNF filter.</p> <p>G1A must withstand a minimum of 50 mmHg pressure in a simulated IVC diameter of 28 mm.</p>

12 APPENDICIES

- 12.1 G1A Recovery Filter Femoral System DV&V Protocol
- 12.2 Manufacturing Documentation
- 12.3 Raw Test Data Recording Sheets
- 12.4 Statistical Analysis Data Sheets
- 12.5 Failure Investigation Report
- 12.6 Modified Recovery Filter Respiratory Fatigue Test - Rationale

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Test Protocol Number

**TPR 04-12-20
REV 0**

**Animal Model Evaluation of
Recovery Filter G1A Femoral System**

Project# 8027

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BPV-17-01-00125562



Test Protocol Number

**TPR 04-12-20
REV 0**

**Animal Model Evaluation of
Recovery Filter G1A Femoral System**

Project# 8027

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1.0 STUDY OBJECTIVES

The objective of this study is to test a new filter and delivery system design *in-vivo* to evaluate; ease and effectiveness of dilator/introducer sheath accessibility, ease and effectiveness of filter advancement/delivery, ease and effectiveness of deployment, placement/deployment accuracy, as well as several other attributes specified in the preliminary PPS070028. This animal study will be a confirmation study whose goal will be to verify the specifications generated from bench testing.

2.0 OVERVIEW/BACKGROUND

2.1 Device Background


The Recovery Filter is a blood clot trapping device designed to prevent pulmonary embolism by mechanical filtration. The filter is implanted percutaneously in the inferior vena cava (IVC). The Recovery Filter has the additional feature of being able to be percutaneously removed after implantation with minimal trauma to the IVC. The Recovery Filter may be used as a permanent filter or be implanted temporarily to treat a temporary risk of pulmonary embolism.

The G1A Recovery Filter (RF-210F) has some changes as compared to the standard Recovery Filter to increase migration resistance and improve centering. These changes include an increased ground wire diameter of the hook from .0085" OD to .0105" OD in order to improve hook strength and migration resistance. The pin outer diameter over which the curvature of the hook is manufactured is still the same at .060" OD. The leg span across the hooks has changed from 30-34mm to 38-42mm in order to improve the ability of the filter to expand with a swelling or bulging vena cava. The centering arm length has increased from .775" long to .990" long and an additional bend applied to the end to improve arm interaction with the vessel wall. The arc of centering arm as it attaches to the sleeve has been modified to have a smooth transition instead of sharp angle. This change was made in order to reduce the stress concentration generated by the sharp angle.

Currently, the Recovery Filter (RF-048F) is deployed via a femoral vein approach using a delivery sheath with the filter mounted on a pusher wire. The new delivery catheter has been modified to increase the delivery sheath distal tip ID and ID under the swaged marker bands to allow for ease of delivery of the G1A filter. Subsequent to the change in sheath tip ID, the OD of the dilator shaft was increased to ensure a smooth transition in profile during sheath placement into the anatomy. Additionally, the mounting spline of the pusher wire has been modified to assist the G1A filter deployment.

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The G1A Recovery Filter Femoral System (catalog # RF-210F) consists of a dilator, a 7 French I.D. introducer sheath, and a delivery catheter. The G1A Recovery Filter is preloaded within the storage tube of the delivery catheter, which consists of pusher pad and spline attached to a pusher wire and handle. The Femoral System is packaged in kits. Kit A consists of a dilator and a 6 French introducer sheath. Kit B consists of the delivery catheter system containing the filter placed within a shipping tray. Each Kit is packaged in a separate unit pouch. Both unit pouches are packaged in a final unit pouch.

2.2 Study Overview

The two sheep will have the following experimental attributes:

On the day of treatment animals will be anesthetized and instrumented. Filters will be deployed in the inferior vena cava.

Sheep 1 and 2: Up to five filters of Design I (Recovery G1A Filter (0.0105" x 0.060")) will be placed in the IVC of each animal model. Test articles will be evaluated immediately following treatment implantation in the vena cava of two sheep.


All filters will be placed under fluoroscopic control. A contrast venogram AP, lateral and/or oblique views will be obtained and fluoroscopic sequences recorded. AP, lateral and/or oblique fluoroscopic sequences will document the positions of the filters.

At the conclusion of the study, a final report will be written including all relevant information specified within this protocol. With the exception of animal and Proposal records, all raw data will be transferred to Bard Peripheral Vascular, Inc from LyChron at the conclusion of the study. Copies of animal and Proposal records will be provided. The Clinical Evaluator(s) may provide procedure details, observations and comments in the form of a report or verbal comments.

3.0 TEST METHOD RATIONALE

The evaluation of catheter-based devices requires an appropriate animal model. Miniature pigs and rabbit models have been widely used but are not appropriate for these devices because of inappropriate (small) vessel size. Consequently, the use of larger animal models, such as sheep, has become more common for this research. The great vessels of the sheep are near the size to those of humans and therefore closely approximate the conditions encountered clinically.

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if a device can be safely deployed in the vena cava of sheep, there is reasonable assurance that the device will perform effectively within the vena cava of humans. Device evaluations within native vessels may not fully approximate device performance, however, the ability to deliver, and visualize system components from native vessels should provide an acceptable level of confidence as to the overall utility of the device if it were used in humans.

4.0 REFERENCE DOCUMENTS

Preliminary Product Performance Specification (PPS070028)
 BOM/Routing Process Report (R5530435)
 USDA Animal Welfare Act (9 CFR, Parts 1, 2 and 3)
 The Guide for Care and Use of Laboratory Animals (ILAR publication, 1996, National Academy Press)

5.0 RESPONSIBILITIES

Animal Care, Preparation and Disposition – LyChron
 Fluoroscopic Lab & Equipment – LyChron
 Filters and Delivery Systems – BPV R&D
 Evaluation of Devices – Physician
 Recording of Data – BPV QA
 Test Report – BPV R&D
 LyChron SOP3015 – Ordering, Assigning and Receiving Animals for Study

6.0 TEST MATERIALS

6.1 Species/Strain, Number and Sex

Two Suffolk sheep will be used in this study. Additional animals may be available for back-up and may be re-assigned to another study if not used. The gender of the test system is not expected to influence the study results and either gender will be used as provided by the animal source. The gender of the animals will be recorded in the final report.


6.2 Source and Experimental History

The animals to be used in this study will be obtained from Pork Power Farms, Turlock, CA. The animals will be experimentally naive at the onset of the study.

6.3 Starting Age and Weight Range

Animals selected for use in this study will be as uniform in age and weight as possible. Their body weights will range from 75-95 kg (target weight is 85 kg), and their age will be commensurate with weight.

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6.4 Identification

Animals will be identified by an ear tag as per LyChron SOP 3015: Ordering, Assigning and Receiving Animals for Studies.

6.5 Sample Units

Ten samples of G1A (.0105"x.060") filters and delivery systems are to be manufactured and packaged according to the redlined procedures outlined in the manufacturing BOM/Routing Process Report (R5530435) and are to be representative of future commercial product. A copy of the redlined procedures will be attached to the Test Report. Therefore, these units will have documented traceability for each component, manufacturing/packaging operation and sterility as required for Design Verification builds. Thereby the documentation of these samples is sufficient to combine this data with future Design Verification and Validation testing.

7.0 **SAMPLE PRECONDITIONING AND TEST ENVIRONMENT**

Following manufacturing, these assembled units will be bulk sterilized (2X) through the same sterilization cycle as the finished units.

The test articles will be stored and prepared in accordance with the Instructions for Use (IFU)

8.0 **EQUIPMENT LIST**

One fluoroscopy unit required (two recommended)
 2 Sheep
 10 Filters and Delivery Systems (RF-210F)
 2 Recovery Cones (RC-15)
 Equipment as specified per IFU
 2 10Fr Sheaths

9.0 **TEST PROCEDURE**

9.1 Test / Control Article Treatment Procedure

The following procedure steps are listed for ease of reference and as a guide to the general procedural progression. Procedure steps may not occur in the exact order as listed.

9.1.1 Animal Pre-Treatment (responsible -LyChron)

On the day of surgery, prepare, anesthetize, and drape animals per LyChron SOPs for aseptic procedures. Animals may be anesthetized via

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mask induction with Isoflurane up to 5% in O₂. Animals are to be weighed. Cephalixin 1 gram IV will be administered prior to filter implantation.


- 9.1.2 Monitor ECG, heart rate, respiration rate, mean arterial pressure, and airway gases. Record parameters as specified in the LyChron SOP, and document approximately every 15-30 minutes during surgical procedures. Additional data (e.g., arterial blood gases, core body temperature) may be obtained per LyChron SOP or at the discretion of the veterinarian or veterinary technician and recorded in the raw data.
- 9.1.3 Perform percutaneous or surgical access of the left common femoral vein and insert the 9F Recovery filter introducer sheath (supplied with test article). A 4F sheath may be placed temporarily prior to introduction of the introducer sheath.
- 9.1.4 Repeat step 9.1.3 using the right common femoral vein.
- 9.1.5 Administer heparin 6000 IU, IV.

NOTE: Sections 9.2.4 and 9.2.6 should be completed by the same physician respectively.

9.2 Test Article Deployment/Evaluation – Animal Model

- 9.2.1 Prepare the test articles in accordance with the Instructions for Use (IFU) and insert the dilator/sheath into the left common femoral vein and advance to the infrarenal inferior vena cava of the animal and record the results on the attached data sheet.
- 9.2.2 A contrast venogram will be performed and recorded. AP and lateral and/or oblique films and/or fluoroscopic sequences will document the intended deployment site of the filters. Exact projection positions will be recorded in the raw data.
- 9.2.3 Measure and record the vessel diameter near the proximal and distal point of the proposed filter deployment site using the internal digital calipers of the fluoroscopy equipment, cardiac review station, or digital hand-held calipers. The guide catheter or sheath in the fluoroscopic images will be used for real-time calibration.

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- 9.2.4 Introduce the filter into the delivery sheath such that the filter sleeve apex aligns with the proximal edge of the distal marker band. Then position the proximal edge of the distal marker band approximately 1 cm below the lowest renal vein. The position of all filters should be measured using the apex of the filter. Pre-deployment vs. post deployment positions will be measured to an appropriate anatomical landmark selected by the physician.

Note: The plan is to recover each filter after placement. If recovery is not possible due to filter tilting or other anatomical challenges impeding the use of the recovery catheter, subsequent filters may be deployed in alternate locations of the vena cava (this may have a negative affect on the result due to differences in anatomy).

- 9.2.5 In the event of vascular spasm or irregularities, or other adverse events, appropriate medications may be administered at the discretion of the Clinical Evaluator (e.g., intravascular nitroglycerin).
- 9.2.6 Deployment of the test article will be assessed fluoroscopically and venogram abnormalities will be noted.
- 9.2.7 Record the observations specified on the data collection sheet (see data sheet attached).
- 9.2.8 Evaluate the access/transition of device #2 using the right common femoral vein. (Do not deploy the filter).
- 9.2.9 Place a 10Fr sheath in the left common femoral vein and continue filter deployment evaluation of devices 2-5 through the 10Fr sheath.
- 9.2.10 Repeat the previous steps for devices 6-10 with the second animal.


9.3 Animal Care

Animal Care is outlined in LyChron SOPs (specifically the Care and Maintenance SOPs for the species being used) and Pork Power Farms Housing Division, Turlock, CA (Extension Facility) SOPs (specifically the Animal Care SOP).

10.0 Statistical Methods

Statistical data analysis will not be applied for this study.

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11.0 Acceptance Criteria

All individual units must meet the User Requirement and Engineering Specification as specified in Table 1 to be deemed acceptable.


Table 1. Acceptance Criteria

Design Characteristic	User Requirement	Engineering Specification
Leading Edge of Dilator/Sheath	The leading edge of the dilator and sheath shall be tapered and smooth.	The leading edge of the dilator and sheath shall be tapered and smooth. (Pass/Fail)
Trackability of Dilator/Sheath over wire	The dilator and sheath must track over the .038" guidewire with minimal resistance.	Minimum Rating of 2 (Scale of 1-4)
Pushability of Dilator/Sheath to implant location	The dilator and sheath must be able to be advanced to the target implant location with minimal resistance.	Minimum Rating of 2 (Scale of 1-4)
Dilator Removal	The dilator must be able to be removed safely with minimal force.	Minimum Rating of 2 (Scale of 1-4)
Filter Hook and Spline Interaction	Filter hooks must not dislodge from the spline during normal shipping or storage.	Filter hooks must not dislodge from the spline during normal shipping or storage. (Pass/Fail)
Filter Advancement into Introducer Sheath	The physician must be able to advance the filter from the storage tube into the introducer sheath with minimal force.	Minimum Rating of 2 (Scale of 1-4)
Filter Advancement Through Introducer Sheath and RO Bands	The physician must be able to advance the filter through the introducer sheath and RO bands.	Minimum Rating of 2 (Scale of 1-4)
Spline Radiopacity	Spline must be radiopaque.	Visible under fluoroscopy. (Pass/Fail)
Ease of Deployment	The physician must be able to deploy the filter with minimal force.	Minimum Rating of 2 (Scale of 1-4)
Filter Deployment Accuracy	The physician must be able to accurately deploy the filter.	Minimum Rating of 2 (Scale of 1-4)
Filter Centering	The filter must self-center within the inferior vena cava.	Minimum Rating of 2 (Scale of 1-4)

Rating Scale:

- 1 – Unacceptable
- 2 – Acceptable
- 3 – Good
- 4 – Excellent/Exceptional

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 BARD PERIPHERAL VASCULAR	Animal Model Evaluation of Recovery Filter G1A Delivery System	TPR 04-12-20 Rev. 0 Page 9 of 10
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12.0 Attachments

12.1 PPS070028 – Preliminary Product Performance Specification

12.2 Data Sheet


Note: Data recording to be done by BPV QA, based on physician comments and assistance from LyChron staff.

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 BARD PERIPHERAL VASCULAR	Animal Model Evaluation of Recovery Filter G1A Delivery System		TPR 04-12-20 Rev. 0 Page 10 of 10

Data Sheet

Animal ID #:	Species: Ovine	Filter ID #:	Fluoroscopy C-Arm ID #:
Animal Weight: ____ kg	Prox. Vessel Dia: ____ mm	Filter Lot #:	Fluoroscopy C-Arm Cal. Due:
Sex (circle one): M / F	Dist. Vessel Dia: ____ mm	Filter Type: .0105x.060	
Implantation Date:		Performed By:	
Leading Edge of Dilator/Sheath	Smooth (Pass/Fail)		
Trackability of Dilator/Sheath over wire	Rating (4-1)		
Pushability of Dilator/Sheath to implant location	Rating (4-1)		
Dilator Removal	Rating (4-1)		
Filter Hook and Spline Interaction	Filter on Spline (Pass/Fail)		
Filter Advancement into Introducer Sheath	Rating (4-1)		
Filter Advancement Through Introducer Sheath and RO Bands	Rating (4-1)		
Spline Radiopacity	Visible (Yes / No)		
Base of Deployment	Rating (4-1)		
Filter Deployment Accuracy	Rating (4-1)		
Filter Centering	Rating (4-1)		

Data Recorded By:			
Data Verified By:			

Rating Scale:

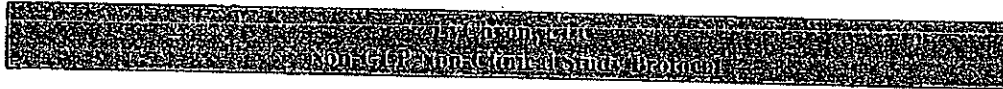
- 1 – Unacceptable
- 2 – Acceptable
- 3 – Good
- 4 – Excellent/Exceptional

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BPV-17-01-00125572



LyChron Protocol Number: 609-P1 Sponsor Protocol Number: TPR-040911

Study title: An Acute and Chronic *In-Vivo* Evaluation of the BARD Recovery® Filter

COPY

PROTOCOL REVIEWED AND APPROVED BY:

Maneesh Taneja, DVM, PhD
Study Director [Signature] 9/22/04
Signature Study Initiation Date

Avijit Mukherjee
Sponsor [Signature] 9/22/04
Signature Date

Brad Hubbard, DVM
LyChron Test Facility Management [Signature] 09/22/04
Signature Date

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PROTOCOL SUMMARY

LyChron ARC Protocol Number	609-P1
Sponsor Protocol Number	TPR-040911
Study Title	An Acute and Chronic <i>In-Vivo</i> Evaluation of the BARD Recovery [®] Filter
Study Duration	Group One: 20 weeks Group Two: 20 weeks
Test Article	Recovery [®] Vena Cava Filter
Test System	Suffolk Sheep
Study Compliance	Non-GLP (Every effort will be made to conduct this study as per GLP regulations with the exception of adding this study to the Master Schedule and Quality Assurance in-phase auditing of the study.) and Pork Power Farms Housing Division, Turlock, CA (Extension Facility)
Sponsor and Sponsor Representative	Representative: Avijit Mukherjee Bard Peripheral Vascular, Inc. 1625 West Third Street Tempe, Arizona 85281 Ph: 480/894-9515 Fax: 480/449-2597
Study Director and Test Facility	Maneesh Taneja, DVM, PhD Email: mtaneja@lychron.com LyChron, LLC 2569 Wyandotte Street Mountain View, CA USA 94043 Ph: 650/938-3675 Fax: 650/938-3450

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BPV-17-01-00125574

Clinical Evaluators	<p>Anthony C. Venbrux, MD Director, Cardiovascular & Interventional Radiology Department of Radiology George Washington University Medical Center 900 23rd St. Ground Floor, Suite 2092, Rm. 112 Washington, DC 20037 202-715-5155</p> <p>John A. Kaufman, MD Chief, Vascular & Interventional Radiology Dotter Interventional Institute Oregon Health & Science University 3181 SW Sam Jackson Park Rd, L-605 Portland, OR 97239-3098 503-494-7660</p>
Pathology Facility Address, Phone, Fax, and E-mail	<p>Pathology Associates, Inc. (PAI) Division of Charles River Laboratories, Inc. 15 Worman's Mill Court, Suite 1 Frederick, MD 21701 Ph. 301-663-1644 Fax 301-663-8994 www.criver.com</p>
Histopathology Facility Address, Phone, and Fax	<p>Pathology Associates, Inc. (PAI) Division of Charles River Laboratories, Inc. 15 Worman's Mill Court, Suite 1 Frederick, MD 21701 Ph. 301-663-1644 Fax 301-663-8994 www.criver.com</p>

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CARR EXHIBIT 54, Page 160

BPV-17-01-00125575

1.0 STUDY OBJECTIVES

The objective of this animal study is to test two new filter designs (I & II) *in-vivo* to evaluate 1) ease of filter removal after an extended (4-12 week) period of time, 2) effect of removal on vena cava wall, and 3) Effect(s) of removal on vena cava wall after different healing periods (8 & 20 weeks). Additionally, secondary subjective observations will be made and recorded regarding 1) ease and effectiveness of filter delivery, 2) ease and effectiveness of deployment, 3) placement/deployment accuracy, and 4) migration resistance.

2.0 SCOPE

Test articles will be evaluated at 4, 12 and 20 weeks in Group 1, and 4, 12 and 20 weeks in Group 2 following treatment implantation in the vena cava of 24 total sheep.

3.0 PROPOSED STUDY SCHEDULE (these dates are estimates)

Initiation of <i>in-vivo</i> implants:	September, 2004
Conclusion of <i>in-vivo</i> study:	March, 2005
Histology Report:	May, 2005
Final Report:	June, 2005 (3-Week after Study Director receives Final Histopathology and Clinical Evaluator/Contributing Scientist Reports)

4.0 DESCRIPTION OF THE TEST SYSTEM**4.1 Species/Strain, Number and Sex**

Approximately twenty four (24) Suffolk sheep will be used in this study. Two additional animals will be available for back-up and will be re-assigned to another study if not used. The gender of the test system is not expected to influence the study results and either gender will be used as provided by the animal source. The gender of the animals used will be recorded in the final report.

4.2 Source and Experimental History

The animals to be used in this study will be obtained from Pork Power Farms, Turlock, CA. The animals will be experimentally naïve at the onset of the study.

4.3 Starting Age and Weight Range

Animals selected for use in this study will be as uniform in age and weight as possible. Their body weights will range from 45-65 kg (target weight is 55 kg), and their age will be commensurate with weight.

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4.4 Identification

Animals will be identified by an ear tag as per LyChron SOP 3015: Ordering, Assigning and Receiving Animals for Studies.

5.0 EXPERIMENTAL DESIGN

5.1 General Description

The two groups will have the following experimental attributes:

Group 1: A single filter of Design I will be placed in the IVC of twelve (12) different sheep (Day 0). Following approximately a 4 week (28 day) residence time, venography will be performed and the filters will be removed from six of the animals. Three of these animals will be euthanized and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by Pathology Associates, Inc. (PAI). The remaining three animals will be returned to housing for an eight-week healing period prior to euthanasia. Following this eight week period, these remaining three animals will undergo repeat venography and then be euthanized and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by an outside laboratory. At 12 weeks, venography will be performed and the filters will be removed from the six remaining animals which were originally implanted at Day 0, three will be euthanized immediately following filter removal and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by an outside laboratory. The three remaining animals will be returned to housing for an additional eight week healing period prior to euthanasia. Following this eight week period, these final three animals will undergo repeat venography and then be euthanized and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by Pathology Associates, Inc. (PAI).

Group 2: A single filter of Design II will be placed in the IVC of twelve (12) different sheep (Day 0). Following approximately a 4 week (28 day) residence time, venography will be performed and the filters will be removed from six of the animals. Three of these animals will be euthanized and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by Pathology Associates, Inc. (PAI). The remaining three animals will be returned to housing for an eight-week healing period prior to euthanasia. Following this eight week period, these remaining three animals will undergo repeat venography and then be euthanized and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by an outside laboratory. At 12 weeks, venography will be performed and the filters will be removed from the six remaining animals which were originally implanted at Day 0, three will be euthanized immediately following filter removal and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by an outside laboratory. The three remaining animals will be returned to housing for an

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additional eight week healing period prior to euthanasia. Following this eight week period, these final three animals will undergo repeat venography and then be euthanized and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by Pathology Associates, Inc. (PAI).

A summary of the above information is outlined in Table 1 (below) and in two separate flowcharts included in the Addendum (A1 & A2). The dates specified may vary by \pm 4 days.

TABLE 1	
DATE	PROCEDURE
Wednesday 9-22-04	Implant 12 sheep with filter Design I (Group 1)
Thursday 10-14-04	Implant 12 additional sheep with filter Design II (Group 2)
Friday 10-22-04	Explant 6 sheep (Group 1A). Euthanize 3 of these. Allow the remaining 3 to heal. Six will be left untouched and kept in housing (Group 1B).
Thursday 11-11-04	Explant 6 sheep (Group 2A). Euthanize 3 of these. Return the remaining 3 to housing.
Thursday 12-16-04	Euthanize remaining 3 sheep (Group 1A). Explant remaining original 6 sheep (Group 1B). Euthanize 3 of these. Allow the remaining 3 to heal.
Thursday 1-6-05	Euthanize remaining 3 sheep (Group 2A). Explant remaining original 6 sheep (Group 2B). Euthanize 3 of these. Allow the remaining 3 to heal.
Sunday 2-13-05	Explant final 3 animals (Group 1B)
Sunday 3-6-05	Explant final 3 animals (Group 2B)

All filters will be placed under fluoroscopic control. A contrast venogram AP, lateral and/or oblique views will be obtained and fluoroscopic sequences recorded. AP, lateral and/or oblique fluoroscopic sequences will document the positions of the filters.

Just prior to filter removal, a contrast venogram will be performed in AP, lateral, and/or oblique views with fluoro recording. All filters will be removed after the specified residence/healing time using the Recovery Cone retrieval system according to the Instructions for Use. Contrast venography will be performed in AP and lateral and/or oblique projections following removal of the filter. Vena cavagrams will be

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evaluated for evidence of extravasations, intimal irregularity or flaps, and vena caval patency.

The IVC will be excised at necropsy and the sites of placement of the Recovery filters (Design I and/or Design II) will be studied grossly and microscopically for evidence of mural hemorrhage, disruption of the IVC, and (where appropriate) aorta, perforation, and inflammation.

At the conclusion of the study, a final report will be written including all relevant information specified in this protocol. With the exception of animal and Proposal records, all raw data will be transferred to Bard Peripheral Vascular, Inc from LyChron at the conclusion of the study (after the final report has been signed off). Copies of animal and Proposal records will be provided. The histology work and final report writing is expected to take eight weeks from the date that the final animal is euthanized. The Clinical Evaluator(s) may provide the procedure details, observations and comments in the form of a report.

On the day of treatment (designated as Day 0) animals will be anesthetized and instrumented. Filters will be deployed in the inferior vena cava.

5.2 Model Justification

The evaluation of catheter-based devices requires an appropriate animal model. Miniature pigs and rabbit models have been widely used but are not appropriate for these devices because of inappropriate (small) vessel size. Consequently, the use of larger animal models, such as sheep, has become more common for this research¹. The great vessels of the sheep are near in size to those of humans and therefore closely approximate the conditions encountered clinically².

If a device can be safely deployed and retrieved from the vena cava of sheep, there is reasonable assurance that the device will perform effectively within the vena cava of humans. Device evaluations within native vessels may not fully approximate device performance, however, the ability to deliver, visualize, and retrieve system components from native vessels should provide an acceptable level of confidence as to the overall utility of the device if it were used in humans.

5.3 Test / Control Article Treatment Procedure

The following procedure steps are listed numerically for ease of reference and as a guide to the general procedural progression. Procedure steps may not occur in the exact order as listed.

5.3.1 Animal Pre-Treatment (responsible -LyChron)

1. On the first day of surgery (designated as Day 0), prepare, anesthetize, and drape animals per LyChron SOPs for aseptic procedures. Animals may be anesthetized via mask induction with Isoflurane up to 5% in O₂. Animals are to be weighed. Cephalexin 1 gram IV will be administered prior to

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filter implantation. Cephalixin 1 gram IV will also be administered prior to filter removal for non-terminal procedures.

2. Monitor ECG, heart rate, respiration rate, mean arterial pressure, and airway gases. Record parameters as specified in the LyChron SOP, and document approximately every 15 – 30 minutes during surgical procedures. Additional data (e.g., arterial blood gases, core body temperature) may be obtained per LyChron SOP or at the discretion of the veterinarian or veterinary technician and recorded in the raw data.
3. Perform percutaneous or surgical access of the common femoral vein and insert the 7 F Recovery filter introducer sheath (supplied with test article). A 4F sheath may be placed temporarily prior to introduction of the introducer sheath. (Note: For follow-up procedures a 5F pigtail catheter will be placed into the vena cava via the femoral vein)
4. Administer heparin 6000 IU, IV.

All filters will be placed under fluoroscopic control. A contrast venogram will be performed and fluoroscopic images recorded. Contrast venography will be performed in AP and lateral and/or oblique projections. Exact projection positions will be recorded in the raw data.

5.3.2 Test Article Deployment and Retrieval (responsible – Sponsor and Clinical Evaluator)

1. Prepare the test articles in accordance with the Instructions for Use (IFU).
2. A contrast venogram will be performed and recorded. AP and lateral and/or oblique films and/or fluoroscopic sequences will document the intended deployment site of the filters. Exact projection positions will be recorded in the raw data.
3. Measure and record the vessel diameter near the proximal and distal point of the proposed filter deployment site using the internal digital calipers of the fluoroscopy equipment, cardiac review station, or digital hand-held calipers. The guide catheter or sheath in the fluoroscopic images will be used for real-time calibration.
4. Introduce the filter and position the device in the infrarenal inferior vena cava with the filter apex approximately 1 cm below the lowest renal vein. Measure and record the exact final position. The final position will be documented in relation to the renal vein or other appropriate anatomical landmarks.
5. In the event of vascular spasm or irregularities, or other adverse events, appropriate medications may be administered at the discretion of the Clinical Evaluator (e.g., intravascular nitroglycerin).
6. Deployment of the test article will be assessed fluoroscopically and venogram abnormalities will be noted.

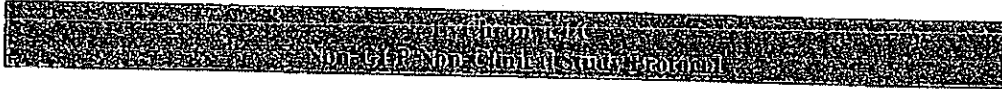
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BPV-17-01-00125580



LyChron Protocol Number: 609-P1 Sponsor Protocol Number: TPR-040911

Study title: An Acute and Chronic *In-Vivo* Evaluation of the BARD Recovery® Filter

COPY

PROTOCOL REVIEWED AND APPROVED BY:

Maneesh Taneja, DVM, PhD [Signature] 9/22/04
Study Director Signature Study Initiation Date

Avijit Mukherjee [Signature] 9/22/04
Sponsor Signature Date

Brad Hubbard, DVM [Signature] 09/22/04
LyChron Test Facility Management Signature Date

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PROTOCOL SUMMARY

LyChron ARC Protocol Number	609-P1
Sponsor Protocol Number	TPR-040911
Study Title	An Acute and Chronic <i>In-Vivo</i> Evaluation of the BARD Recovery [®] Filter
Study Duration	Group One: 20 weeks Group Two: 20 weeks
Test Article	Recovery [®] Vena Cava Filter
Test System	Suffolk Sheep
Study Compliance	Non-GLP (Every effort will be made to conduct this study as per GLP regulations with the exception of adding this study to the Master Schedule and Quality Assurance in-phase auditing of the study.) and Pork Power Farms Housing Division, Turlock, CA (Extension Facility)
Sponsor and Sponsor Representative	Representative: Avijit Mukherjee Bard Peripheral Vascular, Inc. 1625 West Third Street Tempe, Arizona 85281 Pb: 480/894-9515 Fax: 480/449-2597
Study Director and Test Facility	Maneesh Taneja, DVM, PhD Email: mtaneja@lychron.com LyChron, LLC 2569 Wyandotte Street Mountain View, CA USA 94043 Ph: 650/938-3675 Fax: 650/938-3450

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CARR EXHIBIT 54, Page 167

BPV-17-01-00125582

Clinical Evaluators	<p>Anthony C. Venbrux, MD Director, Cardiovascular & Interventional Radiology Department of Radiology George Washington University Medical Center 900 23rd St. Ground Floor, Suite 2092, Rm. 112 Washington, DC 20037 202-715-5155</p> <p>John A. Kaufman, MD Chief, Vascular & Interventional Radiology Dotter Interventional Institute Oregon Health & Science University 3181 SW Sam Jackson Park Rd, L-605 Portland, OR 97239-3098 503-494-7660</p>
Pathology Facility Address, Phone, Fax, and E-mail	<p>Pathology Associates, Inc. (PAI) Division of Charles River Laboratories, Inc. 15 Worman's Mill Court, Suite 1 Frederick, MD 21701 Ph. 301-663-1644 Fax 301-663-8994 www.criver.com</p>
Histopathology Facility Address, Phone, and Fax	<p>Pathology Associates, Inc. (PAI) Division of Charles River Laboratories, Inc. 15 Worman's Mill Court, Suite 1 Frederick, MD 21701 Ph. 301-663-1644 Fax 301-663-8994 www.criver.com</p>

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BPV-17-01-00125583

1.0 STUDY OBJECTIVES

The objective of this animal study is to test two new filter designs (I & II) *in-vivo* to evaluate 1) ease of filter removal after an extended (4-12 week) period of time, 2) effect of removal on vena cava wall, and 3) Effect(s) of removal on vena cava wall after different healing periods (8 & 20 weeks). Additionally, secondary subjective observations will be made and recorded regarding 1) ease and effectiveness of filter delivery, 2) ease and effectiveness of deployment, 3) placement/deployment accuracy, and 4) migration resistance.

2.0 SCOPE

Test articles will be evaluated at 4, 12 and 20 weeks in Group 1, and 4, 12 and 20 weeks in Group 2 following treatment implantation in the vena cava of 24 total sheep.

3.0 PROPOSED STUDY SCHEDULE (these dates are estimates)

Initiation of <i>in-vivo</i> implants:	September, 2004
Conclusion of <i>in-vivo</i> study:	March, 2005
Histology Report:	May, 2005
Final Report:	June, 2005 (3-Week after Study Director receives Final Histopathology and Clinical Evaluator/Contributing Scientist Reports)

4.0 DESCRIPTION OF THE TEST SYSTEM**4.1 Species/Strain, Number and Sex**

Approximately twenty four (24) Suffolk sheep will be used in this study. Two additional animals will be available for back-up and will be re-assigned to another study if not used. The gender of the test system is not expected to influence the study results and either gender will be used as provided by the animal source. The gender of the animals used will be recorded in the final report.

4.2 Source and Experimental History

The animals to be used in this study will be obtained from Pork Power Farms, Turlock, CA. The animals will be experimentally naive at the onset of the study.

4.3 Starting Age and Weight Range

Animals selected for use in this study will be as uniform in age and weight as possible. Their body weights will range from 45-65 kg (target weight is 55 kg), and their age will be commensurate with weight.

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4.4 Identification

Animals will be identified by an ear tag as per LyChron SOP 3015: Ordering, Assigning and Receiving Animals for Studies.

5.0 EXPERIMENTAL DESIGN

5.1 General Description

The two groups will have the following experimental attributes:

Group 1: A single filter of Design I will be placed in the IVC of twelve (12) different sheep (Day 0). Following approximately a 4 week (28 day) residence time, venography will be performed and the filters will be removed from six of the animals. Three of these animals will be euthanized and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by Pathology Associates, Inc. (PAI). The remaining three animals will be returned to housing for an eight-week healing period prior to euthanasia. Following this eight week period, these remaining three animals will undergo repeat venography and then be euthanized and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by an outside laboratory. At 12 weeks, venography will be performed and the filters will be removed from the six remaining animals which were originally implanted at Day 0, three will be euthanized immediately following filter removal and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by an outside laboratory. The three remaining animals will be returned to housing for an additional eight week healing period prior to euthanasia. Following this eight week period, these final three animals will undergo repeat venography and then be euthanized and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by Pathology Associates, Inc. (PAI).

Group 2: A single filter of Design II will be placed in the IVC of twelve (12) different sheep (Day 0). Following approximately a 4 week (28 day) residence time, venography will be performed and the filters will be removed from six of the animals. Three of these animals will be euthanized and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by Pathology Associates, Inc. (PAI). The remaining three animals will be returned to housing for an eight-week healing period prior to euthanasia. Following this eight week period, these remaining three animals will undergo repeat venography and then be euthanized and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by an outside laboratory. At 12 weeks, venography will be performed and the filters will be removed from the six remaining animals which were originally implanted at Day 0, three will be euthanized immediately following filter removal and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by an outside laboratory. The three remaining animals will be returned to housing for an

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additional eight week healing period prior to euthanasia. Following this eight week period, these final three animals will undergo repeat venography and then be euthanized and the portion of the IVC which contained the filter will be perfusion-fixed and harvested for histopathological evaluation by Pathology Associates, Inc. (PAI).

A summary of the above information is outlined in Table 1 (below) and in two separate flowcharts included in the Addendum (A1 & A2). The dates specified may vary by \pm 4 days.

Table 1	
DATE	PROCEDURE
Wednesday 9-22-04	Implant 12 sheep with filter Design I (Group 1)
Thursday 10-14-04	Implant 12 additional sheep with filter Design II (Group 2)
Friday 10-22-04	Explant 6 sheep (Group 1A). Euthanize 3 of these. Allow the remaining 3 to heal. Six will be left untouched and kept in housing (Group 1B).
Thursday 11-11-04	Explant 6 sheep (Group 2A). Euthanize 3 of these. Return the remaining 3 to housing.
Thursday 12-16-04	Euthanize remaining 3 sheep (Group 1A). Explant remaining original 6 sheep (Group 1B). Euthanize 3 of these. Allow the remaining 3 to heal.
Thursday 1-6-05	Euthanize remaining 3 sheep (Group 2A). Explant remaining original 6 sheep (Group 2B). Euthanize 3 of these. Allow the remaining 3 to heal.
Sunday 2-13-05	Explant final 3 animals (Group 1B)
Sunday 3-6-05	Explant final 3 animals (Group 2B)

All filters will be placed under fluoroscopic control. A contrast venogram AP, lateral and/or oblique views will be obtained and fluoroscopic sequences recorded. AP, lateral and/or oblique fluoroscopic sequences will document the positions of the filters.

Just prior to filter removal, a contrast venogram will be performed in AP, lateral, and/or oblique views with fluoro recording. All filters will be removed after the specified residence/healing time using the Recovery Cone retrieval system according to the Instructions for Use. Contrast venography will be performed in AP and lateral and/or oblique projections following removal of the filter. Vena cagrams will be

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evaluated for evidence of extravasations, intimal irregularity or flaps, and vena caval patency.

The IVC will be excised at necropsy and the sites of placement of the Recovery filters (Design I and/or Design II) will be studied grossly and microscopically for evidence of mural hemorrhage, disruption of the IVC, and (where appropriate) aorta, perforation, and inflammation.

At the conclusion of the study, a final report will be written including all relevant information specified in this protocol. With the exception of animal and Proposal records, all raw data will be transferred to Bard Peripheral Vascular, Inc from LyChron at the conclusion of the study (after the final report has been signed off). Copies of animal and Proposal records will be provided. The histology work and final report writing is expected to take eight weeks from the date that the final animal is euthanized. The Clinical Evaluator(s) may provide the procedure details, observations and comments in the form of a report.

On the day of treatment (designated as Day 0) animals will be anesthetized and instrumented. Filters will be deployed in the inferior vena cava.

5.2 Model Justification

The evaluation of catheter-based devices requires an appropriate animal model. Miniature pigs and rabbit models have been widely used but are not appropriate for these devices because of inappropriate (small) vessel size. Consequently, the use of larger animal models, such as sheep, has become more common for this research¹. The great vessels of the sheep are near in size to those of humans and therefore closely approximate the conditions encountered clinically².

If a device can be safely deployed and retrieved from the vena cava of sheep, there is reasonable assurance that the device will perform effectively within the vena cava of humans. Device evaluations within native vessels may not fully approximate device performance, however, the ability to deliver, visualize, and retrieve system components from native vessels should provide an acceptable level of confidence as to the overall utility of the device if it were used in humans.

5.3 Test / Control Article Treatment Procedure

The following procedure steps are listed numerically for ease of reference and as a guide to the general procedural progression. Procedure steps may not occur in the exact order as listed.

5.3.1 Animal Pre-Treatment (responsible -LyChron)

1. On the first day of surgery (designated as Day 0), prepare, anesthetize, and drape animals per LyChron SOPs for aseptic procedures. Animals may be anesthetized via mask induction with Isoflurane up to 5% in O₂. Animals are to be weighed. Cephalexin 1 gram IV will be administered prior to

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filter implantation. Cephalixin 1 gram IV will also be administered prior to filter removal for non-terminal procedures.

2. Monitor ECG, heart rate, respiration rate, mean arterial pressure, and airway gases. Record parameters as specified in the LyChron SOP, and document approximately every 15 – 30 minutes during surgical procedures. Additional data (e.g., arterial blood gases, core body temperature) may be obtained per LyChron SOP or at the discretion of the veterinarian or veterinary technician and recorded in the raw data.
3. Perform percutaneous or surgical access of the common femoral vein and insert the 7 F Recovery filter introducer sheath (supplied with test article). A 4F sheath may be placed temporarily prior to introduction of the introducer sheath. (Note: For follow-up procedures a 5F pigtail catheter will be placed into the vena cava via the femoral vein)
4. Administer heparin 6000 IU, IV.

All filters will be placed under fluoroscopic control. A contrast venogram will be performed and fluoroscopic images recorded. Contrast venography will be performed in AP and lateral and/or oblique projections. Exact projection positions will be recorded in the raw data.

5.3.2 Test Article Deployment and Retrieval (responsible –Sponsor and Clinical Evaluator)

1. Prepare the test articles in accordance with the Instructions for Use (IFU).
2. A contrast venogram will be performed and recorded. AP and lateral and/or oblique films and/or fluoroscopic sequences will document the intended deployment site of the filters. Exact projection positions will be recorded in the raw data.
3. Measure and record the vessel diameter near the proximal and distal point of the proposed filter deployment site using the internal digital calipers of the fluoroscopy equipment, cardiac review station, or digital hand-held calipers. The guide catheter or sheath in the fluoroscopic images will be used for real-time calibration.
4. Introduce the filter and position the device in the infrarenal inferior vena cava with the filter apex approximately 1 cm below the lowest renal vein. Measure and record the exact final position. The final position will be documented in relation to the renal vein or other appropriate anatomical landmarks.
5. In the event of vascular spasm or irregularities, or other adverse events, appropriate medications may be administered at the discretion of the Clinical Evaluator (e.g., intravascular nitroglycerin).
6. Deployment of the test article will be assessed fluoroscopically and venogram abnormalities will be noted.

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7. Record the following observations on the data collection sheet (see Addendum A3): Ease of filter insertion, ease and effectiveness of filter deployment, and placement/deployment accuracy.

5.3.3 Filter Retrieval (Interim Procedure)

1. At the prescribed follow-up timepoint, using sterile technique, anesthetize, instrument and monitor study animals as described in section 5.3.1 for venographic evaluation of the inferior vena cava and filter retrieval. (Obtain the animals weights.)
2. Via percutaneous or cutdown procedures advance a 5F pigtail catheter into the vena cava and perform vena cavagram in AP, Lateral, and/or Oblique views. Exact projection positions will be recorded in the raw data. Note the position and orientation of the filter. Examine the filter for presence of tilting, migration, and thrombus formation. Evaluate the patency of the IVC.
3. Insert the introducer sheath from the Recovery Cone[®] Retrieval System kit into the jugular vein via percutaneous or cut down procedures and access the vena cava.
4. Following the cavagram, remove the filter according to the Recovery Cone Retrieval System IFU. All filters will be removed after the specified residence/healing time using the Recovery Cone retrieval system.
5. Repeat vena cavagram in AP, Lateral and/or Oblique views. Evaluate the vena cavagram for evidence of extravasation, intimal irregularity or flaps, and vena caval patency.
6. Remove the introducer sheath and pigtail catheter. Obtain hemostasis at the access sites via manual pressure or vessel ligation. If vessel access was via cut-down, close the incision site in layers with suture material. Allow the animal to recover from anesthesia.
7. Record the following observations on the data collection sheet (see Addendum A4); Migration resistance.

Following the procedure, and at the discretion of the LyChron veterinary staff, animals will be administered antibiotics and analgesics as necessary (documentation will be included in the animal's records as appropriate).

5.3.4 Filter Retrieval (Non-Terminal Procedure)

1. At the prescribed follow-up timepoint, using sterile technique, anesthetize, instrument and monitor study animals as described in section 5.3.1 for

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venographic evaluation of the inferior vena cava and filter removal.
(Obtain the animals weights.)

2. Via percutaneous or cutdown procedures advance a 5F pigtail catheter into the vena cava and perform vena cavagram in AP, Lateral, and/or Oblique views. Exact projection positions will be recorded in the raw data. Note the position and orientation of the filter. Examine the filter for presence of tilting, migration, and thrombus formation. Evaluate the patency of the IVC.
3. Insert the introducer sheath from the Recovery Cone[®] Retrieval System kit into the right internal jugular vein via percutaneous or cut down procedures and access the vena cava.
4. Following the cavagram, remove the filter according to the Recovery Cone Retrieval System IFU. All filters will be removed after the specified residence/healing time using the Recovery Cone retrieval system.
5. Evaluate the vena cavagram for evidence of extravasation, intimal irregularity or flaps, and vena caval patency.
6. Repeat vena cavagram. Evaluate the vena cavagram for evidence of extravasation, intimal irregularity or flaps, and vena caval patency. Exact projection positions will be recorded in the raw data.
7. Record the following observations on the data collection sheet (see Addendum A4): Migration resistance and ease of removal.
8. Remove the introducer sheath and allow the animal to recover from anesthesia.

5.3.5 Analysis of Test Article Following Retrieval

1. Rinse each filter with saline and inspect visually.
2. Document the absence or presence of thrombus.
3. Obtain macrophotographs. (Include the following information in the picture at a minimum: species, animal number, study #, type of specimen.)

5.3.6 Filter Retrieval (Terminal Procedure)

1. At the prescribed follow-up timepoint, using a clean but not necessarily sterile technique, anesthetize, instrument and monitor study animals as described in section 5.3.1 for venographic evaluation of the inferior vena cava and filter retrieval. (Obtain the animals weights.)
2. Via percutaneous or cut-down procedures advance a 5F pigtail catheter into the vena cava and perform vena cavagram in AP, Lateral, and/or Oblique views. Exact projection positions will be recorded in the raw data. Note the position and orientation of the filter. Examine the filter for presence of tilting, migration, and thrombus formation. Evaluate the vena

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cavagram for evidence of extravasation, intimal irregularity or flaps, and ven caval patency.

3. Insert the introducer sheath from the recovery Cone Retrieval System kit into the jugular vein via percutaneous or cut down procedures and access the vena cava.
4. Following the cavagram, remove the filter according to the Recovery Cone Retrieval system IFU. All filters will be removed after the specified residence/healing time using the Recovery Cone retrieval system.

5.3.6.1 Analysis of Test Article Following Retrieval

1. Rinse each filter with saline and inspect visually.
2. Document the absence or presence of thrombus.
3. Obtain macrophotographs. (Include the following information in the picture at a minimum: species, animal number, study #, type of specimen)
4. Euthanize the animal and harvest the appropriate portion of the vena cava.
5. Collect tissues (Section 5.7) for pathology and histopathology analysis.

5.4 In-life Measurements

5.4.1 Body Weight

On Day 0 of the study each animal will be weighed. Body weights will also be obtained at the time of filter removal and prior to euthanasia.

5.5 Animal Care

Animal Care is outlined in LyChron SOPs (specifically the Care and Maintenance SOPs for the species being used) and Pork Power Farms Housing Division, Turlock, CA (Extension Facility) SOPs (specifically the Animal Care SOP).

5.5.1 Humane Care of Animals and Daily Observations

The Proposal and any amendments or procedures involving the care or use of animals in this study will be reviewed and approved by LyChron's Animal Care and Use Committee (ARC) prior to the initiation of such procedures (i.e., prior to the start of the study for most protocol-specified procedures). Treatment of the animals will be in accordance with LyChron SOPs, which utilize the regulations outlined in the USDA Animal Welfare Act (9 CFR, Parts 1, 2 and 3) and the conditions specified in The Guide for Care and Use of Laboratory Animals (ILAR publication, 1996, National Academy Press) as a guide.

The study animals will be observed at least daily for signs of illness or distress as per LyChron and Extension Facility SOPs, and any such

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observations will be promptly reported to the responsible veterinarian and Sponsor representative. Animal care will be the responsibility of the attending veterinarian at the testing facility and, when applicable, the Extension Facility. The responsible veterinarian may make decisions about treatment of the animal(s) and/or alteration of study procedures, which will be reported to the sponsor. If the condition of the animal(s) warrants significant therapeutic intervention or alteration in study procedures, the Sponsor will be contacted when possible to discuss appropriate action.

5.5.2 Housing and Environmental Controls

Animals will be housed in cages or pens that meet or exceed the weight/space specifications outlined in the Animal Welfare Act Regulations. If appropriate, and at the discretion of a LyChron Veterinarian, animals may be housed in multiples. Pens or cages will be identified as per LyChron and Extension Facility SOPs. The LyChron and Extension Facility housing facilities will provide appropriate ambient lighting and ambient temperature. Animal rooms, pens and cage cleaning will be performed according to LyChron and Extension Facility SOPs.

5.5.3 Food and Water

The animals will be fed and watered as specified in LyChron and the Extension Facility SOPs.

5.6 Disposition of Animals / Method of Euthanasia / Tissue Collection

5.6.1 Early Death/Unscheduled Euthanasia

In the event of an early or unscheduled death, the Study Director in consultation with the Sponsor will determine the need to replace the animal(s). All early or unscheduled deaths will be necropsied as soon as possible by qualified personnel in order to investigate a cause of death. The following cavities and systems may be examined for abnormalities:

- Muscular/skeletal system
- Thoracic cavity
- Abdominal cavity
- Abdominal Vena Cava
- Abdominal Aorta

Any abnormal findings will be documented and the abnormal tissues will be collected and shipped with the appropriate documentation to the Pathology lab as described in section 5.7.1 for evaluation.

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Treated vessels from early or unscheduled deaths will be collected and shipped with the appropriate documentation to the Pathology lab as described in section 5.7.1 and processed as described in section 5.7.2.

5.6.2 Scheduled Euthanasia Timepoint(s)

See Table 1 for the scheduled euthanasia timepoints.

5.6.3 Method of Euthanasia

Animals will be euthanized per LyChron SOPs.

5.7 Pathology and Histology

5.7.1 Gross Necropsy (responsible--Sponsor and LyChron)

All animals will be necropsied as soon as possible after euthanasia or death. A complete gross necropsy (excluding the brain, unless indicated by observations of neurological signs) will be conducted by qualified LyChron personnel or the consulting veterinary pathologist. The necropsy will include examination of:

- Carcass and muscular/skeletal system
- All external surfaces and orifices
- Neck with associated organs and tissues
- Thoracic, abdominal and pelvic cavities with their associated organs and tissues with emphasis on the heart and lungs in the thoracic cavity and the kidneys in the abdominal cavity.

Post euthanasia, the vena cava will be examined for gross abnormalities, photographed, and will be perfusion-fixed under physiologic pressure. The excision will be performed proximal, ensuring that no less than 10 mm of vein (proximal and distal to the filter margins, if applicable) is included. The proximal (toward the heart, away from the legs) portion of the vena cava will be marked with a suture for anatomical orientation. Tissues will be rinsed and placed into individual jars of formalin and labeled, at minimum, with date, study number, species, animal number, specimen, and the initials of the person preparing the specimen.

Ship tissues and copies of appropriate necropsy and treatment documentation overnight to:

Pathology Associates, Inc. (PAI)
Division of Charles River Laboratories, Inc.
15 Worman's Mill Court, Suite I
Frederick, MD 21701
Ph. 301-663-1644 Fax 301-663-8994

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5.7.2 Histological Sample Preparation (responsible -PAI)

Vessel segments at the site of test article treatment, including approximately 10 mm of adjacent proximal and distal vessel (starting from the proximal and distal filter margin, if applicable), will be embedded in paraffin as per the Pathology Facility SOPs. This will ensure that the treatment sites, as well as untreated tissue proximal and distal to the treatment site, are included in the section to be processed. Tissues will be sectioned with a microtome, stained with hematoxylin and eosin and trichrome and examined with a light microscope. The Pathologist will provide photomicrographs of slides and an analysis of presence of mural hemorrhage, disruption of the IVC and (where appropriate aorta, perforation, and inflammation). Tissues from any abnormal findings will be processed as per Pathology Facility SOPs and evaluated by the Pathologist.

6.0 REFERENCES

1. Brountzos EN, Kaufman JA, Venbrux AC, Brown PR, Harry J, Kinst TF, Kleshinski S, Ravenscroft AC. A new optional vena cava filter: retrieval at 12 weeks in an animal model. J Vasc Interv Radiol. 2003 Jun;14(6):763-72.
2. Proctor MC, Cho KJ, Greenfield LJ. Development and evaluation of investigational vena caval filters: the complementary roles of in vitro and in vivo studies. J Surg Res. 2003 Mar;110(1):241-54.
3. Matsuura JH, White RA, Kopchok G, Nishinian G, Woody JD, Rosenthal D, Clark MD. Vena caval filter placement by intravascular ultrasound. Cardiovasc Surg. 2001 Dec;9(6):571-4.
4. Crochet D, Grossetete R, Bach-Lijour B, Larguier L, Le Nihouannen JC. Evaluation of the LGM Vena-Tech infrarenal vena cava filter in an ovine venous thromboembolism model. J Vasc Interv Radiol. 2001 Jun;12(6):739-45.
5. LyChron ARC Proposal #609
6. Animal Welfare Regulations per 9 CFR § 1-3.
7. "Guide for the Care and Use of Laboratory Animals," Institutes of Laboratory Animal Resources, NIH, 1996

7.0 ABBREVIATIONS, ACRONYMS AND SYMBOLS

µg = Micrograms	IV = Intravenous
AP = Anterior-Posterior	Kg = Kilograms
ACT = Activated Clotting Time	mm = Millimeters
cm = Centimeters	NIH = National Institute of Health
CFR = Code of Federal Regulations	OS = per OS, or per orum
GLP = Good Laboratory Practice	SOP = Standard Operating Procedure
IU = International Units	IVC = Inferior Vena Cava

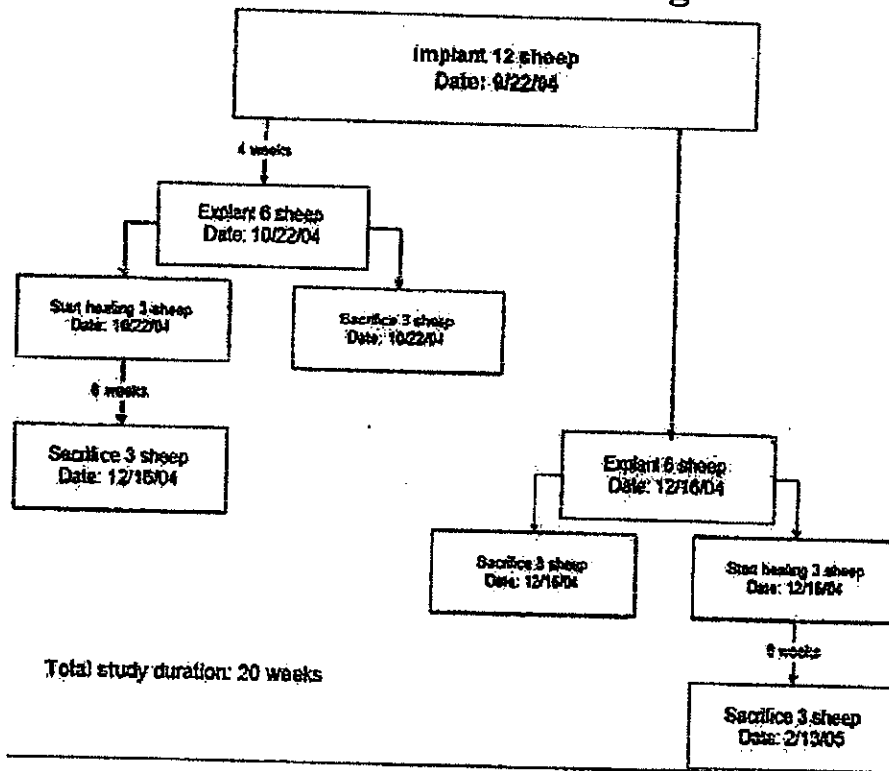
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Addendum

A1: Protocol Flowchart for Design I



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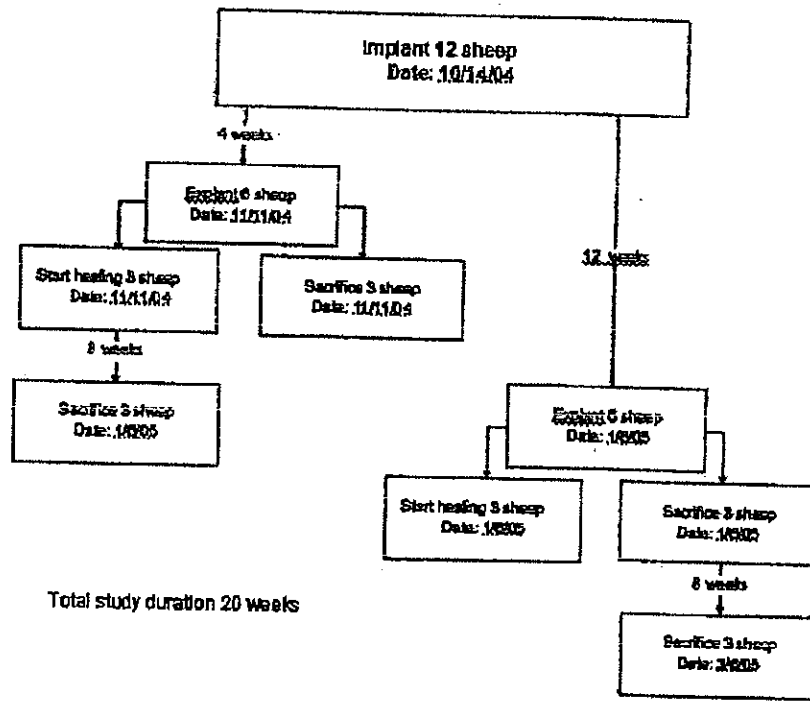
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A2: Protocol Flowchart for Design II



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A3: Data Collection Form - Implantation

An Acute and Chronic *In-Vivo* Evaluation of the BARD Recovery® Filter
(TPR-040911)

Animal ID #:	Species: Ovine	Filter ID #:	
Animal Weight: ____ kg		Filter Lot #:	
Sex (circle one): M / F		Filter Type:	
Implantation Date:			
		Performed By:	
Implantation Observations	Unit of Measurement	Results	Comments
1. Ease of filter delivery:	Rating (4-1)		
2. Ease of filter deployment:	Rating (4-1)		
3. Effectiveness of filter deployment:	Normal/Crossed/Tilted/Other		
4. Placement/Deployment Accuracy:	Millimeters (mm)		

	Print Name:	Signature:	Date:
Data Recorded By:			
Data Verified By:			
Clinical Evaluator:			

Rating Scale:

- 4 = Excellent – No force/effort required
 3 = Good – Minor force/effort required
 2 = Fair – Moderate force/effort required
 1 = Poor – High force/effort required

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A4: Data Collection Form - Removal

An Acute and Chronic *In-Vivo* Evaluation of the BARD Recovery® Filter
(TPR-040911)

Animal ID #:	Species: Ovine	Filter ID #:	
Animal Weight: ___ kg		Filter Lot #:	
Sex (circle one): M / F		Filter Type:	
Removal Date:		Performed By:	
Removal Observations	Unit of Measurement	Results	Comments
1. Filter Migration	Yes/No		
2. Migration Distance (if applicable)	Millimeters (mm)		
3. Filter Configuration	Normal/Crossed /Tilted/Other		
4. Ease of Removal	Ranking (4-1)		
5. Extravisation	Yes/No		
6. Thrombus	Yes/No		
Print Name:		Signature:	Date:
Data Recorded By:			
Data Verified By:			
Clinical Evaluator:			

Rating Scale:

4 = Excellent - No force/effort required 3 = Good - Minor force/effort required
2 = Fair - Moderate force/effort required 1 = Poor - High force/effort required

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Engineering Test Report Number

ETR 05-02-11

REV 0

**G1A Recovery Filter Femoral System Chronic Animal Study
Report**

(Project# 8027)

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1.0 OBJECTIVE/PURPOSE OF TEST

The objective of this study was to test the modified Recovery Filter design *in-vivo* to evaluate; 1) ease of filter removal following 4-week and 12-week indwell times, 2) effects of filter removal on vena cava wall, 3) effect(s) of filter removal on vena cava wall prior to and following 8-week healing period. Additional observations were made and recorded regarding the ease and effectiveness of filter delivery, ease and effectiveness of deployment, placement/deployment accuracy, migration resistance, ease of removal, extravasations, intimal irregularity and caval narrowing. This report includes data on a total of nine (9) sheep – three (3) evaluated after four (4) weeks indwell time, three (3) after eight (8) weeks healing time (following four weeks indwell time) and three (3) after twelve (12) weeks indwell time. The purpose of this study was to test performance of the modified Recovery Filter. The Femoral delivery system used in this study was subsequently modified and tested in an Acute In-Vivo Study (Ref. ETR# 05-01-06). The Pathology Report (ref. attachment 4) provides the results of histopathological evaluation on all nine animals.

2.0 INTRODUCTION/BACKGROUND INFORMATION

The Recovery Filter is a blood clot trapping device designed to prevent pulmonary embolism by mechanical filtration. The filter is implanted percutaneously in the inferior vena cava (IVC). The Recovery Filter has the additional feature of being able to be percutaneously removed after implantation with minimal trauma to the IVC. The Recovery Filter may be used as a permanent filter or be implanted temporarily to treat a temporary risk of pulmonary embolism.

The modified Recovery Filter (RF-210F) has some changes as compared to the currently marketed predicate Recovery Filter to increase migration resistance, increase fracture resistance and improve centering. These changes include an increased ground wire diameter of the hook from .0085" OD to .0105" OD in order to improve hook strength and migration resistance. The pin outer diameter over which the curvature of the hook is manufactured is still the same at .060" OD. The leg span across the hooks has changed from 30-34mm to 38-42mm in order to improve the ability of the filter to expand with a swelling or bulging vena cava. The centering arm length has increased from .775" long to .990" long and an additional bend applied to the end to improve arm interaction with the vessel wall. The arc of centering arm as it attaches to the sleeve has been modified to have a smooth transition instead of sharp angle. This change was made in order to reduce the stress concentration generated by the sharp angle.

Currently, the Recovery Filter (RF-048F) is deployed via a femoral vein approach using a delivery sheath with the filter mounted on a pusher wire.

The modified Recovery Filter Femoral System (catalog # RF-210F) consists of a dilator, a 7 French introducer sheath, and a delivery catheter. The modified Recovery Filter is preloaded within the storage tube of the delivery catheter, which consists of pusher pad and spline attached to a pusher wire and handle. The Femoral System is packaged in kits. Kit A consists of a dilator and a 7 French introducer sheath. Kit B consists of the delivery system containing the filter placed within a shipping tray. Each kit is packaged in a separate unit pouch. Both unit pouches are packaged in a final unit pouch.

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3.0 REFERENCE DOCUMENTS

- TPR-04-09-11 An Acute and Chronic In-Vivo Evaluation of Bard Recovery Filter Protocol (reference attachment 1)
Pathology Report (reference attachment 4)
- ETR 05-01-06 Animal Model Evaluation of Recovery Filter with Modified Femoral Delivery System (Acute Study)
- USDA Animal Welfare Act (9 CFR, Parts 1, 2 and 3)
- The Guide for Care and Use of Laboratory Animals (ILAR publication, 1996, National Academy Press)

4.0 TEST PROCEDURE

The modified Recovery filter and the current Femoral Delivery Systems were tested *in-vivo* in sheep. In all animals, vascular access was made through the common femoral vein and a 7F filter introducer sheath was inserted. All filters were placed in the infrarenal inferior vena cava under fluoroscopic control. Although the exact final position was not measured and recorded on a data sheet at the time of deployment, measurements were taken and landmarks were followed to assess the device migration at the time of retrieval. Contrast vena cavography was performed in AP and lateral and/or oblique projections. Exact projection positions were recorded as raw data.

The filters were removed after the specified residence/healing times (6 @ 4 weeks and 3 @ 12 weeks) using the Recovery Cone according to the Instruction for Use (IFU). Access into the right internal jugular vein was obtained via percutaneous procedure using an appropriate size sheath and a 5F pigtail catheter was advanced into the vena cava. A contrast vena cavagram was performed in AP, lateral and/or oblique views with fluoro recording. Each filter was examined for occurrence of tilting, migration and thrombus. Patency of the IVC was evaluated. The introducer sheath/dilator set from the Recovery Cone kit was inserted into the vena cava via the access obtained above. The filters were removed according to the Recovery Cone IFU. Contrast vena cavography was performed in AP and in lateral and/or oblique projections following removal of the filter and (if applicable) prior to euthanasia following a 8-wk healing period for the animals with 4 weeks indwell time. Vena cavagrams were evaluated for evidence of extravasations, intimal irregularity, and caval narrowing or stenosis.

In accordance with the experimental design, animal numbers 481, 489 and 494 were euthanized on the same day their filters were removed while animal numbers 463, 464 and 467 were allowed to heal for 8 weeks prior to relook and euthanasia. Animal # 465 had to be euthanized at the time of deployment as the complications encountered during the procedure (the filter got stuck in the delivery system because the ID of the introducer sheath under the distal marker band was out of specification). This animal was replaced by animal # 481.

Animal numbers 466, 488 and 490 were euthanized on the same day their filters were removed (following 12 weeks of indwell time).

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Pathology results on all nine animals are included in this report (reference attachment 4).

5.0 TEST MATERIALS

The modified Recovery Filters (.0105"x.060") were manufactured per lot# 08-04-004 and inspected at Bard's Glens Falls facility (according to the Manufacturing Procedure MP 9028) prior to being sent for sterilization, and are representative of future commercial product (reference attachment 2). The delivery systems used in the study were similar to the current Femoral Delivery System with a few modifications, namely a modified pusher pad (0.040" diameter instead of 0.050" diameter) and a modified spline on the pusher wire.

The purpose of this study was to test performance of the modified Recovery filter. The Femoral delivery system used in this study was subsequently modified and tested in an Acute In-Vivo Study (Ref. ETR# 05-01-06).

6.0 NAME & ADDRESS OF TEST FACILITY


LyChron LLC
 2569 Wyandotte St.
 Mountain View, CA 94043

7.0 TEST RESULTS/SUMMARY OF DATA

A summary of the vessel measurements during the study are shown in Table 1. Copies of raw data following implantation, removal and relook for each filter shown in this table are attached (ref. attachment 8).

Table 1: Summary of vessel measurements

Animal ID#	Gender	Device ID#	Observation Point	Weight (kg)	IVC diameter with lateral and anterior-posterior (AP) contrast venography projections			
					IVC Pre AP (mm)	IVC Post AP (mm)	IVC Pre Lateral (mm)	IVC Post Lateral (mm)
463	F	5	Implantation	45.4	11.59	17.52	9.16	10.02
			Removal	55.0	11.28	12.06	11.47	9.77
			Relook	56.4	N/A	12.33	N/A	11.25
464	M	9	Implantation	54.6	18.56	18.67	17.96	18.99
			Removal	59.4	17.23	12.18	11.07	10.00
			Relook	67.8	N/A	14.34	N/A	12.59
465	M	*18	Implantation	49.8	19.78	N/A	15.58	N/A

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467	F	15	Implantation	53.8	22.16	20.23	30.75	32.50
			Removal	53.6	19.30	20.17	15.81	16.16
			Relook	56.0	N/A	19.16	N/A	15.04
481	M	3	Implantation	56.0	17.6	16.5	11.8	14.3
			Removal	54.6	18.39	16.85	13.32	10.56
			Relook	N/A	N/A	N/A	N/A	N/A
489	M	13	Implantation	49.6	17.38	23.75	9.93	13.72
			Removal	55.0	11.92	12.07	11.71	11.75
			Relook	N/A	N/A	N/A	N/A	N/A
494	M	12	Implantation	47.0	12.54	20.34	8.80	23.03
			Removal	49.8	16.52	15.83	14.13	14.76
			Relook	N/A	N/A	N/A	N/A	N/A

Notes: a*. Device# 18 was deployed with complications (filter got stuck in the delivery system). Animal # 465 was euthanized on the table. A device failure analysis report was completed by Sponsor (see attachment 3).

Table 2a: Test device evaluations and clinical observations performed during the deployment.

Animal ID	Test device evaluations/ clinical observations at filter implantation			
	Ease of filter delivery (*Rating 4-1)	Ease of filter deployment (*Rating 4-1)	Effectiveness of filter deployment (Normal/Crossed/Tilted/Other)	Placement/ Deployment Accuracy (mm)
463	3	3	Normal	Within 2 mm
464	3	3	Normal	*Within 0 mm
^b 465	4	1	^c N/A	N/A
467	4	3	^e Tilted	Within 2 mm
481	4	4	Normal	Within 2 mm
489	3	3	Normal	Within 1 mm
^d 494	4	3	Normal	Within 2 mm

***Rating Scale:**

4 = Excellent – No force/effort required 3 = Good – Minor force/effort required
2 = Fair – Moderate force/effort required 1 = Poor – High force/effort required


General comments recorded during procedure:

^aPerfect deployment accuracy.

^bModerate to severe resistance from the skin to the sheath (unrelated to the filter).

^cNon-deployment. Animal scratched from follow-up.

^dTip of sheath cut off just behind the distal marker band. Difficulty in disengaging legs from spine. Feed popped out of sheath with 2 mm cephalad migration.

 PERIPHERAL VASCULAR	G1A Recovery Filter Femoral System Chronic Animal Study Report	ETR 05-02-11 Rev. 0 Page 7 of 11
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Comments made by the Sponsor Engineer at the review of procedure cavagram (OEC) recordings of the study animals performed retrospectively to assess the Effectiveness of Filter Deployment:

^aTilting occurred presumably due to the inability of the delivery system to release the filter in a timely manner. The physician retracted the pusher wire before the hooks were completely released from the spline. The delivery system has since been modified by the sponsor and the likelihood of such tilting reoccurring has been minimized with those modifications.

Table 2b: Test device evaluations and clinical observations performed during the removal.

Animal ID	Test device evaluations/ clinical observations at filter removal			
	Filter Migration	Migration Distance	Filter Configuration (Normal/Crossed/Tilted/Other)	Ease of Removal (*Rating 4-1)
463	Yes	^a 10 mm caudal	Normal	^b 3
464	Yes	3 mm cranial	Normal	^b 3
465	N/A	N/A	N/A	N/A
467	No	0 mm	Tilted	^c 1
481	No	0 mm	Normal	^d 3
489	Yes	5 mm caudal	Normal	^b 3
494 ^c	No	0 mm	Normal	^b 3

***Rating Scale:**

4 = Excellent – No force/effort required 3 = Good – Minor force/effort required

2 = Fair – Moderate force/effort required 1 = Poor – High force/effort required

General comments recorded during procedure:

^aDoes not exclude sub-contraction from parallax.

^bMore force required than for current commercial device.

^cRequired spiral shaped catheter (KUMPE).

^dUsed guidewire.

Table 2c: Test device evaluations and clinical observations performed following the filter removal.

Animal ID	Test device evaluations/ clinical observations following filter removal			
	Extravasations	Thrombus	Intimal Irregularity/ Flaps	Caval Narrowing/ Stenosis
463	No	^a Yes	No	^b Yes
464	No	No	No	No
465	N/A	N/A	N/A	N/A
467	No	^c Yes	^d Yes	No
481	No	No	No	^a Yes
489	No	^f No	No	No
494 ^c	No	^b Yes	No	No

General comments recorded during procedure:

^aApex filter less than 20%.

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^bEstimate 30%.

^cIn IVC (mural) after removal. Clot in filter after removal.

^dMural thrombus (probably traumatic during difficult retrieval).

^e10-20%.

^fNormal fibrinous material at Apex.

^gLess than 15% in filter Apex.

Table 2d: Clinical observations performed prior to euthanasia of the group of animals that were allowed to heal for 8 weeks after the filter removal.

Animal ID	Clinical Observations prior to euthanasia			
	Extravasations	Thrombus	Intimal Irregularity/ Flaps	Caval Narrowing/ Stenosis
463	No	No	No	No
464	No	No	No	No
467	No	No	No	No

8.0 PROTOCOL DEVIATION


The animal study protocol (ref. attachment 1) includes evaluation of two designs of the modified Recovery Filter, termed Design I and Design II. Based on feasibility bench testing data and animal study results, it was decided to pursue Design I for commercialization.

The design of this study is similar to the study that was conducted in support of K031328 with the exception of a 30 day time point instead of an intra-procedural time point (0 day). The initial plan, as stated in the animal study protocol (ref. attachment 1), was to include histopathology data on twelve animals. Since the damage to the IVC wall and lack of extravasation upon explant of the modified Recovery Filter was consistent with the findings of the previous study, a decision was made to truncate the study at twelve-week indwell time in support of the Special 510(k) submission.

In summary, this report contains histopathology data on nine sheep as shown below:

- > Three sheep (#481, 489, 494) explanted at four weeks and sacrificed
- > Three sheep (#463, 464, 467) explanted at four weeks, healed for eight weeks and sacrificed
- > Three sheep (# 466, 488, 490) explanted at twelve weeks and sacrificed

Tips of the introducer sheath were cut off just behind the distal marker band of the delivery systems for filter numbers 466, 488 and 490 after a delivery failure was experienced for filter# 465. The introducer has since been modified to incorporate a larger inside diameter.) The Acute Animal Study (ref. ETR 05-01-06) was successfully performed with a modified Femoral Delivery System which incorporates this change.

 PERIPHERAL VASCULAR	G1A Recovery Filter Femoral System Chronic Animal Study Report	ETR 05-02-11 Rev. 0 Page 9 of 11
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9.0 DISCUSSION OF RESULTS

The force required to deploy the modified Recovery® Filter (test article) was acceptable and appeared to the physician investigators to be similar to the currently marketed predicate Recovery Filter (RF 048F). The modified Recovery Filter could be introduced into the delivery sheath from the storage tube consistently and smoothly. Advancement of the filter to the end of the sheath required little force. The actual deployment, in which the pusher wire is held in place and the sheath withdrawn to expose the device, required an acceptable amount of force. In one instance, (animal #465) a filter was not deliverable as the feet became stuck within the delivery sheath at the level of the distal marker band. Analysis of this device and sheath revealed that the diameter of the lumen of the sheath at this level was below that required in the specifications. The investigators were satisfied that this was the cause of the delivery failure. The delivery sheath has since been modified to minimize the likelihood of such occurrence in the future. This was confirmed in satisfactory performance of the modified Femoral Delivery System in the Acute Animal Study (ref. ETR 05-01-06).

The accuracy of deployment of the test article was considered acceptable by the physician investigators. The physician investigators could not detect any difference in accuracy of deployment between the modified Recovery filter and the currently marketed predicate Recovery filter. The four-week follow-up cavagrams were compared directly to the post-placement images by both physician investigators at the time of filter retrieval. There were no instances of significant filter migration. In three animals (#463, 464, and 489) there was apparent minor caudal migration (1 cm or less). In the case of the 1 cm caudal migration, the physician investigators concluded that some component optical parallax contributed to this apparent migration, and that the actual distance moved was probably less. The physician investigators were satisfied that the modified Recovery Filter maintained a stable position within the inferior vena cava.

The retrieval technique for the modified Recovery Filter (test article) is similar to the currently marketed predicate Recovery Filter. In animal #467, the filter was found to be tilted at the time of retrieval, resulting in a prolonged procedure with multiple catheter manipulations. The filter was successfully retrieved, although some caval intimal irregularity and mural thrombus were noted after retrieval that had not been present on the pre-retrieval cavagram. This was attributed to the catheter manipulations. Difficult retrievals are occasionally encountered with the currently marketed device; however, in animal #467, tilting has occurred presumably due to the inability of the delivery system to release the filter in a timely manner. The delivery system has since been modified by the Sponsor and the likelihood of such tilting reoccurring is minimized with those modifications.

The force required to disengage the test device from the wall of the IVC for retrieval was considered to be minor with the exception of animal #467. In this case the retrieval was rated as "Poor" due to the tilting of the filter. Both physician investigators felt that the force required to retrieve the test device was higher than that required for the currently marketed predicate Recovery filter. Neither physician investigator considered this to be of clinical concern. With the exception of animal #467, the IVC appeared normal in the immediate post-retrieval cavagrams.

 Mediant PERIPHERAL VASCULAR	G1A Recovery Filter Femoral System Chronic Animal Study Report	ETR 05-02-11 Rev. 0 Page 10 of 11
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Vessel measurements, test device evaluations and clinical observations performed during and following filter removal and prior to euthanasia are provided in this report for animals # 463, 464, 467, 481, 489, 494 as shown in Tables 1, 2a, 2b, 2c and 2d in section 7.0 Test Results/Summary of Data (pages 5 through 9).

10.0 Pathology Report

(Reference attachment 4)

This report prepared by Pathology Associates Division of Charles River Laboratories, Inc., presents the results of the gross and macroscopic evaluation of nine segments of inferior vena cava (IVC) in which a modified Recovery Filter had been implanted and then removed. In six of these animals (#463, 464, 467, 481, 489, 494), the device had been in place for 4 weeks prior to removal. Three of these six animals (#463, 464, 467) were sacrificed at four weeks. The remaining three animals (#481, 489, 494) were sacrificed after an eight week healing period. In animals # 466, 488 and 490, the device had been in place for 12 weeks prior to removal. These animals were sacrificed immediately following filter explantation and their vena cavae were removed (reference attachment 5: "Protocol Flowchart for Design I").

Results of gross macroscopic and microscopic evaluation of nine segments of inferior vena cava (IVC) have demonstrated that the modified Recovery Filter can be percutaneously delivered in sheep IVC and be removed using Recovery Cone after 4 weeks and 12 weeks of filter indwell time. Removal can be reliably accomplished without significant damage to the IVC wall. These results confirm that the effects of removal from the sheep IVC of the modified Recovery Filter are similar to the currently marketed predicate Recovery Filter.

11.0 Conclusions

Provided by the physician investigators (reference: attachments 6 and 7)

This study initiated 22 September 2004 at LyChron, LLC (Mountain View, CA) was carefully performed. The modified Recovery[®] Filter design was the test article. The physician investigators were pleased with the results and felt that there is a substantial improvement in the design without compromising the overall function of the filter. We observed: 1) no caval occlusion/thrombosis, 2) minimal migration (some slight movement of which may be actually imaging centering in a growing animal, 3) accurate deployment, 4) no obvious IVC perforations, 5) no contrast extravasations from the IVC after filter removal, and 6) no hemodynamically significant caval stenosis. One animal had to be euthanized because of a problem with a deployment sheath (not the filter itself). The force required to remove this group of modified Recovery Filters was greater than the predicate Recovery Filter thereby resulting in score values of 3's in Table 2b (rating scale: 4-1, where 4= excellent - no force/effort required; 3= good - minor force/effort required; 2= fair - moderate force/effort required; 1= poor - high force/effort required)

 BARD PERIPHERAL VASCULAR	G1A Recovery Filter Femoral System Chronic Animal Study Report	ETR 05-02-11 Rev. 0 Page 11 of 11
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In summary, the modified Recovery® Filter (test article) performed in an acceptable fashion and similar to the currently marketed device (predicate Recovery Filter) with the exception of the force required for retrieval. The physician investigators feel that this animal study will serve as a basis for documenting device design improvements. Such improvements will further benefit patients with thrombo-embolic disease.

Results of gross macroscopic and microscopic evaluation of nine segments of inferior vena cava (IVC) have demonstrated that the modified Recovery Filter can be percutaneously delivered in sheep IVC and be removed using Recovery Cone after 4 weeks and 12 weeks of filter indwell time. Removal can be reliably accomplished without significant damage to the IVC wall. These results confirm that the effects of removal from the sheep IVC of the modified Recovery Filter are similar to the currently marketed predicate Recovery Filter.

12.0 Attachments

Attachment 1 - TPR-04-09-11 An Acute and Chronic in-Vivo Evaluation of the modified BARD Recovery Filter Protocol

Attachment 2 - BARD incoming Inspection Physical Property Data (MP 9028) for modified Recovery Filter

Attachment 3 - Study TPR-04-09-11; Animal Study Reject Filter (Device Failure Investigation Report)

Attachment 4 - Pathology Report Study# TPR-04-09-11; Prepared by Charles River Laboratories, Pathology Associates Division

Attachment 5 - Protocol Flowchart for Design I (shows animal #'s sacrificed on specific dates)

Attachment 6 - Physician Investigator's comments (Drs. John Kaufman)

Attachment 7 - Physician investigator's comments (Dr. Anthony Venbrux)

Attachment 8 - Raw data following implantation, removal and relook of modified Recovery Filter in animal numbers 463, 464, 467, 481, 489, 494, 466, 488 and 490

Appendix 7

CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER

CARR EXHIBIT 54, Page 195

BPV-17-01-00125610

Traditional 510(k)
Recovery[®] Filter with Femoral Delivery

Page 3

Appendix 7. -- *In-vivo* Non-Clinical Protocol and Report

Bard Peripheral Vascular, Inc

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CARR EXHIBIT 54, Page 196

BPV-17-01-00125611

Traditional 510(k)
Recovery[®] Filter with Femoral Delivery

Page 4

A copy of the *in-vivo* Non-Clinical Protocol and Report is provided on the attached CD-ROM.

Bard Peripheral Vascular, Inc

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BARD

CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER

CARR EXHIBIT 54, Page 197

BPV-17-01-00125612

Appendix 8

CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER

Traditional 510(k)
Recovery[®] Filter with Femoral Delivery

Page 5

Appendix 8: Material Certification

Bard Peripheral Vascular, Inc

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CARR EXHIBIT 54, Page 199

BPV-17-01-00125614

Traditional 510(k)
Recovery[®] Filter with Femoral Delivery

Page 6

Material Certification

Component Certification

The components and material compositions of the predicate and subject devices are identical and are described in Table 1.

Table 1. Predicate and Subject Device Components and Materials

Component	Material
(b)(4)	

Device Certification

All of the materials used to fabricate the subject device are identical to the final sterilized predicate device in formulation, processing, and sterilization, and no other chemicals have been added (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents, etc.).

Bard Peripheral Vascular, Inc

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BARDD

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CARR EXHIBIT 54, Page 200

BPV-17-01-00125615

EXHIBIT M

(Exhibit 2)

(Filed Under Seal)

EXHIBIT N

(Exhibit 2)

(Filed Under Seal)

EXHIBIT O

(Exhibit 2)

(Filed Under Seal)

EXHIBIT P

(Exhibit 2)

(Filed Under Seal)

EXHIBIT Q

(Exhibit 2)

IN THE CIRCUIT COURT OF THE
SEVENTEENTH JUDICIAL CIRCUIT, IN
AND FOR BROWARD COUNTY,
FLORIDA

CLARE AUSTIN,

Case No: CACE-15-008373

Plaintiff,

vs.

C.R. BARD, INC., a foreign corporation,
and BARD PERIPHERAL VASCULAR,
INC., an Arizona corporation.

Defendants.

**PLAINTIFF'S MEMORANDUM MOTION *IN LIMINE* No. 4:
REGARDING FDA 510(k) CLEARANCE AND LACK OF FDA ENFORCEMENT**

Plaintiff seeks a pretrial ruling to preclude (1) evidence and argument relating to FDA's 510(k) clearance of Bard's IVC filters; and (2) evidence on the lack of FDA enforcement against Bard in connection with its filters.¹ This is an issue of extraordinary importance.

1. In previous arguments and trials Bard has attempted to assert an "FDA defense," implying that FDA clearance to sell its IVC filters demonstrates filter safety/efficacy and that its conduct as a manufacturer was reasonable. Bard has sought to adorn this argument with evidence that FDA has not taken enforcement action in connection with its G2 line of filters.

2. However, the 510(k) clearance process does not demonstrate safety or efficacy and FDA's lack of enforcement does not support an inference that Bard filters are safe or that Bard has acted reasonably. The evidence would be misleading and its introduction would create a distracting "mini-trial" on FDA compliance, as other courts have recognized.

¹ Plaintiff incorporates the facts described in her Omnibus Memorandum of Facts and Law filed herewith.

EXHIBIT R

(Exhibit 2)

Bard's Exhibits By Category - Communications With or About FDA Contacts 1999 - 2016

510(k) Filter Submissions	510(k) Non-Filter Submissions	Letters Regarding Substantial Equivalence, or Inability to Determine Substantial Equivalence	Administrative or Logistical Communications	Interactions Pertaining to General Controls, Under the Act or Regulations		Deficiency Notifications to Bard	Bard Responses to Deficiencies	Bard Internal Notes/Emails
(Exhibit #)	(Exhibit #)	(Exhibit #)	(Exhibit #)	(Exhibit #)		(Exhibit #)	(Exhibit #)	(Exhibit #)
C-1	C-89	C-7	C-13	C-3	V-3	C-2	C-9	C-5
C-6	C-99	C-12	C-20	C-4	V-15	C-10	C-11	C-8
C-14	C-115	C-21	C-32	C-15	V-38	C-46	C-47	C-29
C-43/C54	C-125	C-23	C-48	C-16	V-39	C-59	C-60	C-33
C-102	V-32	C-58	C-49	C-17	V-45	C-84	C-85	C-35
C-104		C-67	C-52	C-18	V-50	C-93	C-95	C-36
C-121		C-98	C-61	C-19	V-53	C-94	C-97	C-38
V-5		C-100	C-62	C-22	V-54	C-96	C-108	C-40
V-32		C-103	C-64	C-24	V-55	C-105	C-113	C-42
V-66a		C-114	C-65	C-25	V-56	C-109	C-118	C-44
V-66b		C-119	C-68	C-26	V-57	C-116	C-123	C-51
V-66c		C-124	C-76	C-27	V-58	C-117	C-127	C-53
V-66d		C-126	C-79	C-28	V-59	C-122	V-8	C-56
V-66e		C-128	C-80	C-30	V-60	V-6	V-10	C-70
V-66f		V-36	C-81	C-31	V-64	V-12	V-11	C-86
V-66g		V-79	C-90	C-34	V-65	V-33	V-18	C-110
V-66h			C-106	C-37	V-67	V-73	V-19a	C-120
V-66i			C-107	C-39	V-68		V-19b	V-1
V-66j			C-111	C-41	V-70		V-19c	V-2
V-66k			C-112	C-45	V-71		V-19d	V-4
V66-l				C-50	V-72		V-20	V-7
				C-55	V-73		V-22	V-9
				C-57	V-74		V-23	V-13
				C-63	V-75		V-24	V-14
				C-66	V-76		V-25	V-16
				C-69	V-77		V-26a	V-17
				C-71	V-78		V-26b	V-19a
				C-72	V-80		V-27	V-19b
				C-73			V-28	V-21
				C-74			V-29	V-37
				C-75			V-34	V-40
				C-77			V-35	V-41
				C-78			V-48	V-42
				C-82			V-49	C-43
				C-83			V-51	V-44
				C-87			V-52	V-47
				C-88			V-69	
				C-91				
				C-92				
				C-101				
22	5	16	20	68		17	37	36

C = Carr V=VanVleet

EXHIBIT S

(Exhibit 2)

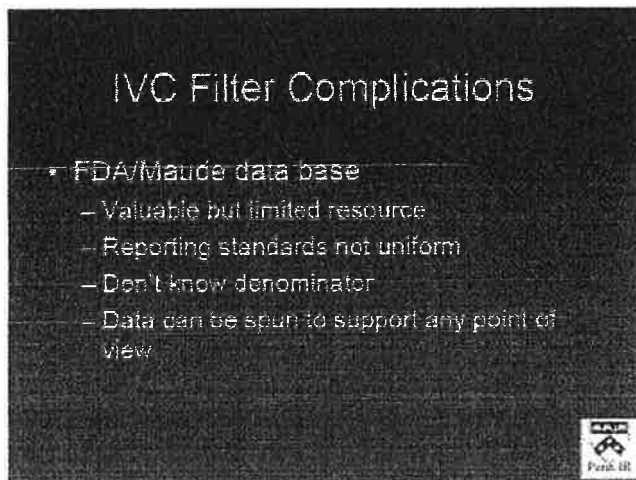
Jamie Price

From: "Greer, Jason"
Sent: Saturday, July 16, 2005 9:38 AM
To: "Alpe, Nicole"; "Baklik, Nancy"; "Cheek, Westy"; "Collins, Greg"; "Dirtadian, JoAnn"; "Gillette, Brooke"; "MacIntyre, Matt"; "Young, Chris"
Cc: "DeLeon, Robert"; "Hudnall, Janet"
Subject: Westy's situation...everyone's situation
Attachments: maude strav sir 2005.png; MAUDE JVIR Nov04.pdf; maude sir 2005 strav.ppt; sir 05 lin maude.jpg

Team:

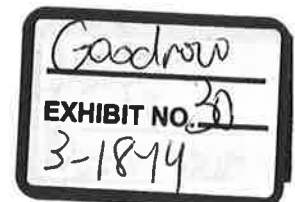
Westy is currently doing battle with one of her large filter accounts. Cordis has brought forward the Maude database to her physicians and caused a problem. We now need to respond. This is Westy's problem today but it could very easily be your problem tomorrow. Cordis has got to sell something. Fox Hollow is eating their lunch in SFA stents, Trapease isn't growing anymore, CQ/Cutting balloon are raining on their PTA parade, Guidant took all their carotid momentum, and SCIRROCO proved they have no advantage of drug-eluting in SFAs. They might very well be on the prowl (you think we've had a rough six months? Go ask your Cordis counterpart).

In the SIR presentations, I found the attached presentation on filters. The presentation was given by Dr. Stravropolous, a partner of Dr. Trerotola at Penn. The study is pretty unremarkable so I haven't included the whole thing. However, it does provide another piece of expert opinion on the value of looking at the Maude database...there is none.



The key point is this: Reporting standards are not uniform and data can be spun (SPUN AS IN Cordis is spinning the Maude database information) to support any point of view. Just a reminder of the things you can also point to should you get hit with this:

- The recent journal article addressing the uselessness of determining complications rates using Maude database that was sent out about 6 months ago. The above presentation is a more recent confirmation from a thought leader that this is true. Proof of this is that on one hand, Westy's Cordis rep has convinced Dr. Cohen that their might be a concern and Dr. Lin's SIR 2005 presentation (sir 05lin maude) shows the Recovery is in line with the rest of the filters.
- Remind the physician: "What has your experience been?". Most people that bring this up as a result of one of our competitors haven't had many problems.
- Anecdotal physicians in your territory that are using it and continue using it.



10/18/2010

BPV-DEP-00005665

LMD1

- Why is Cordis bringing this forward? Are they trying to sell you the Trapease or try to get you to stop putting Recovery in? Is this about patient care or the reps paycheck? (If your reps name is Charles: Is this about patient care or Charles Care?)
- "Most of the bariatric patients getting filters are getting RF. We know from our caval distention discussion (you do remember that conversation, right?) a couple of weeks ago that these patients are problematic, right? Well, regardless of what filter all these bariatric patients had in them, chances are, the would have had these exact same complications. When you take out bariatric complications, our complications rates are lower than the other companies. How many bariatric patients are you putting filters in? If you are doing them and you are concerned, may I suggest the safest filter on the market that has been on the market for the longest time in its current form... The Simon Nitinol?"
- If you want a filter that will give you the greatest chance of reducing your complications, The Simon Nitinol is that filter. (I have a spreadsheet from Maude that shows this).

I hope this information helps and serves as a reminder to all.

Pro-Act ...don't re-act.



Jason Greer

District Sales Manager- Lone Star Region
jason.greer@crbard.com www.bardpv.com
(877) 478-1281 fax (800) 657-1498

10/18/2010

BPV-DEP-00005666

LMD1

EXHIBIT T

(Exhibit 2)

(Filed Under Seal)

EXHIBIT U

(Exhibit 2)

Guidance for Industry and FDA Reviewers/Staff

Guidance for Cardiovascular Intravascular Filter 510(k) Submissions

Document issued on: November 26, 1999

This document supersedes document Guidance for the Submission of 510(k) Premarket Notifications for Cardiovascular Intravascular Filters, February 11, 1997.



U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Interventional Cardiology Devices Branch
Division of Cardiovascular and Respiratory Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to, Donna Buckley, Center for Devices and Radiological Health, 9200 Corporate Boulevard, HFZ-450, Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Donna Buckley at (301) 443-8243.

Additional Copies

World Wide Web/CDRH home page: <http://www.fda.gov/cdrh/ode/24.pdf>, or CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111, specify number 024 when prompted for the document shelf number.

Guidance¹ for Cardiovascular Intravascular Filter 510(k) Submissions

This guidance document describes a means by which cardiovascular intravascular filter devices may comply with the requirement of special controls for class II devices. Designation of this guidance document as a special control means that manufacturers attempting to establish that their device is substantially equivalent to a predicate cardiovascular intravascular filter device should demonstrate that the proposed device complies with either the specific recommendations of this guidance or some alternate control that provides equivalent assurances of safety and effectiveness.

I. Scope:

This draft guidance has been developed in an attempt to identify important preclinical tests and clinical design considerations for cardiovascular intravascular filters (filters). This guidance addresses filters that are permanently implanted in the inferior vena cava for the purpose of preventing thromboemboli generated in the lower limbs from flowing into the right side of the heart and the pulmonary circulation. It is limited in scope to those filters that are designed in such a way as to be seated within the vena cava via a series of hooks which are at the end of several legs or struts which converge at an apex. Filters that have a design that significantly differs from this may require premarket approval and submission of a premarket approval application (PMA) or a completed product development protocol (PDP). This guidance is further limited to filters indicated for use for the prevention of recurrent pulmonary embolism via placement in the vena cava in the following situations:

- Pulmonary thromboembolism when anticoagulants are contraindicated
- Failure of anticoagulant therapy in thromboembolic diseases
- Emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced
- Chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated

Manufacturers who wish to pursue other indications should contact FDA to determine the data necessary to support a new indication and the appropriate regulatory pathway.

II. Introduction

Pulmonary embolism (PE) is a serious clinical issue causing significant morbidity and mortality. It has been estimated that more than 600,000 cases of clinically significant PE occur and result in

¹ This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

approximately 200,000 deaths annually in the United States^{2,3,4}. The patient often survives the first embolism but is at high risk that a second fatal PE will occur. PE recurs in approximately 6% to 25% of treated patients². Additionally, the incidence of PE in patients with deep venous thrombosis (DVT) is 19% to 28%⁵. Treatment of PE has been shown to be effective in reducing the mortality from 30% to 8%¹. Normally, patients with DVT and, or PE are treated with anticoagulation therapy. However, in some patients anticoagulation is ineffective, contraindicated or results in complications which require that it be discontinued. For these patients, vena caval interruption with a filter is recommended. The goal of filter placement is to try to obtain high filtering efficiency (large and small emboli) without impedance of blood flow and with reduced device related thrombosis while minimizing migration and without penetration of the vessel wall.

The following are the criteria for an ideal filter:

- Nonthrombogenic
- High filter efficiency without impedance of blood flow
- Secure fixation within the vena cava
- Rapid and safe percutaneous insertion
- Low rate of associated morbidity
- Magnetic resonance imaging (MRI) compatibility

The necessary array of tests for a particular filter will depend, in part, on the specific design. Therefore, this document may not reflect the complete battery of pre-clinical testing necessary to qualify all filters/designs. However, there are certain aspects of filter design that are general in nature and should be assessed. The degree to which a proposed device is similar to a currently marketed filter will indicate the level of testing necessary, i.e., whether the design characteristics can be assessed via *in vitro* bench testing, *in vivo* animal testing, clinical testing or some combination of all three.

² Dalen, J.E. and J.S. Albert, "Natural history of pulmonary embolism," *Progressive Cardiovascular Diseases*, 17:259-270, 1975.

³ Smith B.A., "Vena Caval Filters," *Emergency Medicine Clinics of North America*, Vol. 13, No.3:645-654, 1994.

⁴ Nunnelee, J.D., and A. Kurgan, "Interruption of the inferior vena cava for venous thromboembolic disease," *Journal of Vascular Nursing*, 11:80-2, 1993.

⁵ Mohan, C.R., J.J. Hoballah, W.J. Sharp, T.F. Kresowik, C.T. Lu and J.D. Corson, "Comparative efficacy and complications of vena caval filters," *Journal of Vascular Surgery*, Vol.21 No. 2:235-246, 1995.

III. Pre-Clinical Testing

A. Biocompatibility

Biocompatibility testing should be conducted in accordance with FDA guidance document "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing", which includes an FDA matrix that designates the type of testing needed for various medical devices. Cardiovascular intravascular filters are defined as permanent implant, blood-contacting devices.

B. Filter Performance

Below is an outline of the general issues that need to be addressed when seeking premarket clearance for a filter. It is the submitter's responsibility to conduct testing which adequately addresses the concerns outlined below as well as any others which may arise due to the unique design of the given device. The goal of this outline is to identify the objective(s) of the pre-clinical test. Test protocols and acceptance criteria for these tests are the responsibility of the submitter. FDA recognizes that there are many different testing methods that may be used to satisfy the objective(s). Where appropriate, some of these tests may be combined. These tests may best be carried out in bench top models or in animal models or in a combination of both. FDA advises that prior to the initiation of animal studies, the submitter should contact FDA and discuss the proposed animal study to ensure general agreement on the adequacy of the animal study protocol.

All tests should be performed on filters fabricated by representative manufacturing processes. An adequate number of samples should be tested. The objectives, test methodologies, results, and conclusions should be clearly defined for each test performed. The performance specifications, test conditions and acceptance criteria for all tests should be completely explained and justified by comparison to expected clinical conditions. Where appropriate, testing should be conducted in an environment simulating clinical conditions. The results of all tests should be reported in a statistically meaningful format, i.e., specification of the number of samples, range of values, mean, standard deviation, and a 95 percent confidence interval where appropriate. A probability measure that is indicative of the statistical significance of any comparisons made should be provided.

1. Simulated deployment

An assessment of the ability to completely deploy the filter reliably in the chosen location under simulated clinical conditions should be made. This test should take into consideration the various routes by which the filter can be introduced into the patient, e.g., femoral, jugular, etc. Although it is recognized that the left femoral route is the most tortuous, all labeled routes should be examined.

2. Introducer/sheath suitability

The objective(s) of this test should be to demonstrate that the sheath will adequately resist kinking when used in the most tortuous pathway. In addition, all bonds of the introducer/sheath should be assessed for their pull strength.

3. Clot trapping ability

This test should demonstrate that the device can capture clinically significant emboli yet still permit sufficient blood flow around trapped emboli without caval occlusion. It should also examine whether the filter achieves this efficiency immediately post-deployment. If it does not, the time period necessary to achieve full filtering efficiency should be characterized.

4. Filter fracture

The filter's response to worst-case respiratory and diaphragmatic movements in the vena cava under simulated respiratory cycles should demonstrate sufficient fatigue resistance of the filter design. In addition, there should be an examination of corrosion resistance and weld strength following cycling.

5. Caval perforation/filter migration

This test should demonstrate that the filter fixes itself within the vena cava at the deployment site and undergoes sufficient endothelialization. The force necessary for device fixation should be characterized over the range of labeled inferior vena cava (IVC) diameters. In addition, this force should not suggest a tendency to perforate the caval wall.

6. Thrombogenicity

The thrombogenic potential of the filter should be examined. This test should demonstrate that the effect of the device on the blood flow would not be sufficient to cause stasis, which could lead to thrombus formation in and around

the device.

7. MRI compatibility

The extent to which the filter is compatible with MR imaging should be assessed (see the Attachment).

IV. Clinical Investigations

It is anticipated that human clinical investigations could be necessary in the development of a “new” vena cava filter to establish its equivalency to currently marketed filters. Such a study may also be necessary for a modified filter design. The need for such a study should be discussed with FDA prior to submission of an investigational device exemption (IDE) application. In those cases in which a study is deemed necessary, the sponsor should carefully consider the following items:

- the appropriate study design
- the study hypothesis
- appropriate sample size
- definitions of success and failure
- the clinically relevant endpoints necessary for the demonstration of substantial equivalence

For the indications outlined previously, the risks and benefits to the patients are well documented. The intent of the clinical study should be to demonstrate that the rates of complications for the investigational filter are comparable to other marketed vena cava filters. Although the risks themselves are well described in the literature, the definitions and methods used to determine the rates are inconsistent and highly variable. Therefore, it is critical to prospectively define and identify the methods of analysis for each potential complication. The complications identified and analyzed during the course of the clinical investigation should include the following:

1. Complications during filter insertion

In the course of trying to place the filter in the vena cava the following

complications have been noted^{6,7}:

- Sheath perforation
- Introducer tip detachment
- Guidewire kinking
- Sheath kinking

These complications can result in⁸:

- Filter deformation
- Fracture
- Premature release or insufficient opening
- Improper placement
- Thrombus formation which may result in insufficient opening

There have also been reports of problems with⁹:

- Filter sticking to and/or getting caught in the introducer while the device is being deployed
- Practitioner difficulty with inserting and/or retrieving failed insertions of the device
- Filter legs breaking during insertion
- Deployment within the introducer
- Breakage of the filter /filter legs upon placement of the device in the patient

The protocol should identify these potential complications and ensure that they will be captured by the investigator on the appropriate data collection forms.

2. Recurrent pulmonary embolism

Patients who present with symptoms suggestive of recurrent PE should undergo a lung scan and/or an arteriogram. If recurrent PE is confirmed, a contrast vena cavogram should be performed to check for any clot within the filter. Some of the

⁶Becker, D.M. et al., "Inferior Vena Cava Filters Indications, Safety, Effectiveness," *Archives of Internal Medicine*, 152:1985-1994,1992.

⁷Greenfield, L.J., et. al., "Extended evaluation of the titanium Greenfield vena caval filter," *Journal of Vascular Surgery*, September 1994:458-465.

⁸Bergqvist,D., "The Role of Vena Caval Interruption in Patients with Venous Thromboembolism," *Progress in Cardiovascular Diseases*, 37(1):25-37,1994.

⁹ FDA MDR database

mechanisms, which may be responsible for PE after filter insertion, are the following⁸:

- Ineffective filtration
- Continuous growth of trapped thrombi through the filter
- Development of thrombosis on the proximal end of the filter
- Filter migration to a position where it does not function optimally
- Filter retraction from the caval wall at thrombus retention (occurring if some of the hooks have grasped the thrombus, which creates a channel between the filter and the caval wall)
- Embolization through collaterals that may be lumbar
- Embolization that may occur via the ovarian/spermatic veins
- Embolization from thrombi proximal to the filter (arm veins, renal or hepatic veins, the right heart)
- Incorrect position of the filter

For those patients who experience a recurrent PE, every attempt should be made to determine the probable mechanism.

3. Death

Deaths attributable to filter complications have been reported to result from:

- cardiac arrest immediately following filter placement
- misplacement of the filter during insertion
- cephalic migration of a filter to the heart after placement.

All patients with suspected filter complications who died during the clinical investigation should undergo an autopsy. A complete report of the findings should be provided for review.

4. Filter migration

Minor filter migration in the caudal or cephalic direction is commonly reported and does not appear to be associated with clinically significant events. The walls of the vena cava are known to move with respiration and changes in intra abdominal pressure induce flexion on the limbs of the filter. The filter may appear to have migrated due to x-ray equipment variation, patient position, measurement error, and respiration. Much of the reported filter movement may actually be due to measurement error resulting from differences in patient positioning, breathing, and parallax. True migration may be caused by an excessively large vena cava, inadequate positioning and massive embolization into the filter with caval dilatation⁸. It is recommended that any movement of the filter with relation to the spine that is 5 mm or greater be recorded as filter migration. Assessment of distal migration should be determined from post implant and follow-up anterior-posterior and lateral films after correction for magnification. When follow-up images are

obtained, efforts should be made to closely reproduce patient positioning and patient respiration to reduce errors in the interpretation of filter migration.

5. Caval penetration

Determination of caval penetration is complicated. Examination via cavography may show filter hooks or legs outside the flow of contrast. This is not necessarily due to penetration. It may be due to endothelialization or tenting of the vena cava or locations in tributary veins. Computed tomography (CT) scans can be used to help rule out some false positives. After correction for magnification, filter base diameter from hook to hook should be recorded from both the implant and follow-up plain films. If an increase in filter base diameter of ≥ 5 mm is recorded, a CT scan should be performed to confirm or exclude the position of filter legs outside of the inferior vena cava. Any other changes, which may be suggestive of possible filter leg penetration of the vena cava, should trigger a CT scan, regardless of increase in the filter base diameter.

6. Filter tilting and angulation

The significance of tilting and angulation of caval filter after placement is controversial. There is a theoretical loss of filtering efficacy of any filter when tilted or angulated significantly; however there is no good clinical data to support a definite increased incidence in PE or failure to trap thrombi. All instances of tilting or angulation should be noted as well as any associated clinical sequelae.

7. Caval occlusion

Caval occlusion is related to filter thrombogenicity, design and flow patterns⁸. Small or moderate sized emboli trapped in a filter are usually asymptomatic since the residual patency of the vena cava and the normal paravertebral collateral veins permit adequate venous return. A large trapped embolus or a cluster of small emboli may occlude a filter completely and thus block the vena cava. After a period of days or weeks, the occlusion occurs and causes a sudden swelling of both lower limbs. In almost all cases the symptoms of IVC occlusion are transient and resolve almost completely within a few weeks or a few months since the thrombi undergo spontaneous lysis. Since it is often clinically difficult or impossible to distinguish IVC filter occlusion from extension of the preexisting DVT because the symptoms may be similar, all instances should be recorded as occlusion unless the extension of DVT can be ruled out.

8. Filter embolization

The risk of filter embolization is primarily limited to the first two weeks after implantation. Embolization of the filter is a serious complication with variable clinical

consequences, comparable to pulmonary thromboembolism. These range from being totally asymptomatic to sudden death. Therapy also ranges from no therapy to open chest surgery and removal of the device. All cases of filter embolization should be recorded and the reasons for occurrence immediately assessed. The subsequent treatment should also be described in detail.

9. Other risks

Complications that occur at the puncture site such as: hematoma formation and A-V fistula, DVT at the puncture site, pneumothorax and air embolism after jugular insertion, should all be recorded on data collection forms and analyzed.

IV. Labeling

The Division of Cardiovascular, Respiratory and Neurological Devices (DCRND) of the Office of Device Evaluation (ODE) conducted a review of the labeling for marketed cardiovascular intravascular filters (vena cava filters). Based on that review, the Food and Drug Administration (FDA) believed that several changes should be made to existing labels to ensure consistency among device manufacturers and to facilitate appropriate use of the devices clinically.

The following sections of the labeling were affected:

- Indications for use
- Contraindications
- Warnings

The Attachment contains a copy of the labeling format developed for this device.

ATTACHMENT

INDICATIONS FOR USE

The labeling should include the following text:

The [NAME OF DEVICE] is indicated for the prevention of recurrent pulmonary embolism via placement in the vena cava in the following situations:

- **pulmonary thromboembolism when anticoagulants are contraindicated;**
- **failure of anticoagulant therapy in thromboembolic diseases;**
- **emergency treatment following massive pulmonary embolism where anticipated benefits of conventional therapy are reduced; and**
- **chronic, recurrent pulmonary embolism where anticoagulant therapy has failed or is contraindicated.**

CONTRAINDICATIONS

The labeling should include the following contraindication:

Vena Cava filters should not be implanted in patients with risk of septic embolism.

Your labeling may include other contraindications which are specific to your particular device design.

WARNINGS

The labeling should include information regarding the use of the device in patients undergoing magnetic resonance imaging (MRI). The following terminology should be used:

MRI-Safe: No additional risk to the patients, but may affect the quality of the diagnostic information.

MRI-Compatible: MRI-Safe and neither interferes with nor is affected by the operations of a MRI device.

Non-Compatible: Neither MRI-Safe nor MRI-Compatible and should not be used in conjunction with MRI systems.

Data to support the chosen warning should be included in your 510(k) notification.

EXHIBIT V

(Exhibit 2)

(Filed Under Seal)

EXHIBIT W

(Exhibit 2)

BARD RECOVERY® G2® FILTER STUDY EVEREST FINAL STUDY REPORT

Title: Bard Recovery® G2® Filter Study (EVEREST)
Final Study Report

Short Title: EVEREST Final Study Report

Protocol Number: BPV-RC-1332

IDE Number: G050134

Product: Bard Recovery® G2® Filter System

Short Product Name Recovery® G2® Filter

Sponsor: Bard Peripheral Vascular, Inc.
1625 West 3rd Street
Tempe, Arizona 85281

Initial Enrollment: December 7, 2005
Final Enrollment: July 24, 2006
Final Retrieval Date: January 29, 2007
Final Follow-up Date: April 5, 2007

Principal Investigator: John A. Kaufman, MD
Chief of Vascular and Interventional Radiology
Dotter Interventional Institute
Oregon Health and Science University
Portland, OR 97239

Sponsor Signatory: David Ciavarella, MD
Staff Vice President, Corporate Clinical Affairs
C.R. Bard, Inc
730 Central Avenue
Murray Hill, NJ 07974
Tel: (908) 277-8306

Good Clinical Practices: This study was conducted in compliance with
applicable FDA requirements for Investigational
Device Exemptions

Date of Report: October 11, 2007

Confidentiality Statement

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EVEREST FINAL STUDY REPORT SYNOPSIS

INTRODUCTION:

This report documents the clinical investigation of 100 subjects enrolled under IDE G050134 who underwent placement and—in a subset of cases—retrieval of the Bard Recovery® G2® Filter System (Recovery® G2® Filter). The Recovery® G2® Filter System has previously received 510(k) clearance for use as a permanent implant, and the Recovery Cone® Removal System is a 510(k) exempt device for use in retrieving vena cava filters (VCFs).

STUDY DESIGN: (SEE SECTION 3)

The Bard Recovery® G2® Filter Clinical Study (EVEREST) was a prospective, multi-center, single arm clinical study designed to assess the safety of retrieval of the Recovery® G2® Filter. The EVEREST study enrolled 100 subjects who were at temporary, increased risk of PE requiring IVC interruption, and for whom Recovery® G2® Filter retrieval could reasonably be expected to occur within 6 months of device placement.

Recovery® G2® Filter retrievability was assessed by the following primary endpoints:

- Technical Success (Retrieval)
- Clinical Success (Retrieval)
- Adverse Events through 30 Days Post-Retrieval

as well as by relevant retrieval procedural parameters and outcomes.

The overall clinical experience was assessed by the following secondary endpoints:

- Filter migration > 2 cm
- Filter fracture as assessed at explant by the Investigator.

as well as by relevant placement procedural parameters and outcomes.

Study procedures consisted of the initial screening and enrollment phase followed by placement of the Recovery® G2® Filter. The follow-up phase began immediately after device placement. Subjects remained hospitalized per standard hospital procedure, and were then discharged to clinical care. During the follow-up phase, all subjects were eligible for Recovery® G2® Filter retrieval. Those subjects who met the retrieval eligibility criteria, and were determined by the Investigator to be appropriate for Recovery® G2® Filter retrieval, underwent the protocol-specified retrieval procedure and data gathering.

INVESTIGATIONAL DEVICES: (SEE SECTION 4.1)

The investigational devices were:

- The Bard Recovery® G2® Filter System, comprised of:
 - The Recovery® G2® Filter
 - The Recovery® G2® Delivery System
- The Recovery Cone® Removal System

STUDY ACCOUNTABILITY: (SEE SECTION 5)

Eleven Investigators at 11 Sites enrolled a total of 100 study subjects between December 7, 2005 and July 24, 2006. Through study completion 3 subjects withdrew informed consent and 6 subjects died. The remaining 91 subjects (58 Retrieved Subjects and 33 Non-Retrieved Subjects) were alive and available for follow-up assessments.

Retrieved Subjects were to be followed for 1 month after the successful filter retrieval procedure. At study completion, filter retrieval had been attempted in 61 subjects, 58 of whom (95.1%) had the filter successfully retrieved. Overall, 96.6% of Retrieved Subjects had an assessment at the protocol specified final follow-up evaluation point.

Non-Retrieved Subjects were to be followed for 6 months after the initial filter placement procedure. Subjects were declared “non-retrieved” for the purposes of this study if their filter was not retrieved by their study exit date. At study completion, 42 subjects were non-retrieved (39 without an attempt and 3 with failed attempts), of whom 6 subjects had died and 3 subjects had withdrawn consent. Overall, 93.9% of the 33 Eligible Non-Retrieved Subjects had an assessment at the protocol specified final follow-up evaluation point.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS: (SEE SECTION 5.5)

Males comprised 67% of the study enrollment and females 33%. The mean age of all 100 enrolled subjects was 52.1 ± 16.7 years (range 19 – 82). The median BMI's were 28.1 for men and 27.3 for women. Thirty nine percent (39%) of all subjects were classified as obese (BMI > 30).

Anticoagulant, antiplatelet and thrombolytic agents were used by substantial numbers of subjects within 7 days of the implantation procedure, including unfractionated heparin by 25% (25), low molecular weight heparin by 38% (38), aspirin by 9% (9), clopidogrel by 1% (1), coumadin by 15% (15) and the class of thrombolytics by 2% (2).

Of the 100 subjects who underwent Recovery® G2® Filter placement in this clinical study, 43% were defined as having active thromboembolic disease (the presence of DVT or PE within 3 months of study enrollment). Most of these subjects (25% of the total subjects) had a contraindication to anticoagulation, 4% had a complication related to the use of anticoagulant medication, 3% had a failure of anticoagulation and 11% had a filter placed without contraindication, complication or failure related to anticoagulant medication. Of the 57% of study subjects without active thromboembolic disease most (49% of total subjects) had no history of any thromboembolic disease and 8% had a history of thromboembolic disease more than 3 months prior to enrollment.

EVALUATION OF RETRIEVAL OF THE RECOVERY® G2® FILTER: (SEE SECTION 6)

Recovery® G2® Filter retrieval was effective.

Technical Success (Retrieval) in retrieving the Recovery® G2® Filter was achieved in 95.1% (58 / 61, 95% CI 86.3 – 99.0%) of study subjects undergoing a retrieval procedure. The 3 failures resulted from embedding of the filter apex in the vena cava wall, which prevented the Recovery Cone® from engaging the filter.

Clinical Success (Retrieval) was achieved in 93.4% (57 / 61, 95% CI 84.1 – 98.2%) of subjects undergoing a retrieval procedure, as one Technical Success (Retrieval) subject had a post-retrieval vena caval stenosis possibly related to a complex but successful retrieval procedure.

Recovery® G2® Filter retrieval was safe. Nine (9) of 61 subjects undergoing a retrieval procedure had 15 adverse events occurring at the time of retrieval through 30 days post filter retrieval procedure, giving an adverse event rate through 30 days of 14.8% (95% CI 7.1 – 26.6%). Four (4) of these events occurred the day of the retrieval procedure; 2 of which were SAEs (vena caval stenosis > 50% and respiratory failure). Of these four events, one was related to the filter, one was related to the Recovery Cone®, one was related to the retrieval procedure, and one as related to an intercurrent condition. The remaining 11 events (2 SAEs and 9 AEs) occurred during the period after the procedure through 30 days post-retrieval, and none (0%) of these adverse events were device- or procedure-related.

Recovery® G2® Filter retrieval could be performed after many months. The mean filter indwell time in the 58 Retrieved Subjects was 140.0 ± 62.1 days (median 143.5, range 5 – 300).

Recovery® G2® Filter retrieval was fast. The mean procedure duration was 30 minutes with minimal fluoroscopy exposure.

Recovery® G2® Filter retrieval was complete and had minimal impact. All 58 (100%) of retrieved filters had intact arms and legs, and there were only 2 (3.3%) post-retrieval procedure-related IVC abnormalities reported for 61 subjects undergoing an attempted retrieval.

CLINICAL EXPERIENCE: THE RECOVERY® G2® FILTER: (SEE SECTION 7)

The Recovery® G2® Filter System performed well as a vena cava filter.

Recovery® G2® Filter placement was fast, with a mean procedure duration of 21.9 minutes and a mean fluoroscopy exposure of 3.2 minutes.

Recovery® G2® Filter placement was easy, with minor procedural observations noted regarding the Delivery System in 8 procedures and the Filter in 6 procedures.

Recovery® G2® Filter placement was acutely successful and accurate, with 100% successful deployment using the first device and 94% deployment in the intended position.

The Recovery® G2® Filter was effective, providing immediate mechanical protection against PE at the conclusion of the procedure. Technical Success (Placement) was achieved in 100% of cases and Clinical Success (Placement) was maintained in 79%. Three (3, 3%) of 100 study subjects had a PE during study follow-up: one subject had a PE 12 days post filter implantation with clot in both legs, the left upper extremity and the left internal jugular vein, one subject had a PE 15 days post filter implantation with no clot in the legs but with clot in the right cephalic vein, and one elderly subject with a PE 17 days after placement without further diagnostic assessment due to multi-system organ failure and withdrawal of medical care.

The Recovery® G2® Filter was safe, with a filter migration rate of 12.2% (all caudal in direction), fracture rate of 1.2%, filter tilt > 15° rate of 18.1% and an IVC penetration rate of 21.7%, all without clinical sequelae except for one subject whose attendant discomfort associated with observations of penetration and tilt > 15° was resolved with a successful filter retrieval, and a second subject whose difficult retrieval procedure associated with observations of migration and tilt > 15° resulted in caval stenosis requiring prolonged hospitalization. All these rates (except for filter tilt which is not covered) are well within the SIR standard anticipated rates for this and similar devices (Grassi et al, 2003). Of the 62 secondary device observations, 93.5% can be classified as Minor Complications of Type A or B according to the current ACR / SIR Practice Guidelines (American College of Radiology, 2005).

GENERAL REVIEW OF ADVERSE EVENTS: (SEE SECTION 8)

The general safety experience in this often seriously ill medical/surgical population requiring protection from PE was quite unremarkable. Seventy six (76) subjects had one or more adverse events during study follow-up; 3% of these events were related to filter placement and 14% were related to the filter itself. Forty nine (49) subjects had one or more SAEs; none of these events were related to either the placement or retrieval procedures and only 6% of these events were related to the filter.

Six (6) study subjects had serious adverse events that were adjudicated to be device-related: two PEs (one with a second possible source above the filter and one with no documented source in an elderly male on a ventilator), an IVC occlusion, a vena caval stenosis (possibly related to a difficult but successful retrieval procedure), a DVT, and one subject with discomfort due to IVC penetration requiring filter removal. In addition to the two device-related PEs mentioned above, there was an additional, non-device-related PE with a clear source above the filter in a subject who was shown to be negative for lower extremity DVT. In all 3 PE cases the filter was free of migration, fracture, tilt > 15°, or penetration.

Six (6) study subjects died during follow-up of pre-existing or intercurrent conditions; none of these were filter-related deaths.

OBESE SUBJECTS: SUBSET ANALYSIS: (SEE SECTION 9)

There was a trend towards a lower rate of Technical Success (Retrieval) in study subjects with BMIs > 30 (88.0% versus 100.0%, $p = 0.064$). There was no appreciable difference between the two BMI groups in the rates of Clinical Success (Retrieval) and Adverse Events through 30 Days Post-Retrieval. No consistent trends were present between the two post hoc groups when comparing death, the occurrence of SAEs or device / procedure related SAEs, or filter migration, fracture, tilt > 15° or penetration. Covariate analyses demonstrate no reliable association between measures of obesity and the outcomes of migration, tilt and penetration.

CONCLUSION:

The goal of this investigation and related analyses was to generate valid scientific evidence in support of a finding of substantial equivalence for this device when used as a retrievable filter. The primary study outcomes show that the Recovery® G2® Filter can be implanted for several months in a relevant patient population and then be retrieved in a

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brief minimally invasive procedure, thus demonstrating the safety and effectiveness of the Recovery® G2® Filter and the Recovery Cone® Removal System when used in a clinically relevant population.

The overall study results constitute valid scientific evidence regarding the overall performance of the Bard Recovery® G2® Filter System as an IVC filter, and serve as a valid basis for comparison in determining that the Recovery® G2® Filter System is substantially equivalent to similarly marketed devices.

EXHIBIT X

(Exhibit 2)

Health Hazard Evaluation

DATE: December 17, 2004

TO: Doug Uelmen, BPV QA

FROM: David Ciavarella, M.D.

RE: Recovery® Filter – Consultant's report

Summary: Seventy-six reports of potentially serious hazards have been reported; 32 of these were judged to be serious, and 10 reports were associated with patient death. Total Recovery filter sales during this reporting period (through December 13, 2004) are 20,827 units. Reporting rates of death and other potentially serious complications for the Recovery filter remain below those reported in the literature. However, literature data are not directly comparable to these reporting rates. An analysis of reporting rates of serious adverse events for all inferior vena cava filters, as determined by analysis of the MAUDE and IMS databases by a consultant, revealed that reporting rates for Recovery are significantly higher than other filters. However, these databases are subject to known, significant biases that make calculation or comparison of incidence rates among products unreliable and inadvisable (according to experts and the FDA). Nevertheless, the number of reported complaints, and the size of the differences between Recovery and other filters, warrant further investigation.

Conclusion: The Frequency category for serious injury (Critical Severity rating) is Occasional (32/20,827, or 0.153%). The Frequency category for non-serious injury (Marginal Severity rating) is Occasional (44/20,827, or 0.21%).

Description of the Problem: Based on awareness of reports of patient death associated with migration of the Recovery inferior vena cava (IVC) filter, Bard requested an independent study of the risks and benefits of the Recovery filter, with an emphasis on its use in bariatric surgery and trauma patients. A consultant was retained for this purpose. The consultant's assignment had three components: 1) Perform a literature review of the risks and benefits of IVC filters, with an emphasis on bariatric surgery and trauma patients; 2) Review internal complaint files for the Recovery filter, and compare its reported adverse events rates to those of competitors' IVC filter by use of the MAUDE and IMS (sales) databases or other means; & 3) develop options for clinical studies that might provide information required to assess the risks and benefits of use of the Recovery filter.

The consultant made the following points:

- 1) The existing literature is of poor quality, with insufficient randomized, controlled trials (RCT) to definitively establish the effectiveness of IVC filters. However, widespread consensus exists in the medical community, obtained via clinical studies of lower credibility than the RCT (such as case reports, case series and prospective non-randomized studies of small size) and expert opinion, that IVC filters lower the likelihood of death from pulmonary embolus in patient groups thought to be at highest risk of this manifestation of venous thromboembolic disease. These high risk groups include patients who have already had a pulmonary embolus or in whom standard anticoagulation therapy cannot be given. However, the existing literature contains comparatively little information on a new generation of IVC filters, especially those with a removability feature (Recovery, Cook Tulip™ and Cordis OptEase™).

Proper product comparisons can be only be drawn from clinical studies where patient populations are carefully defined, comparisons are made under controlled circumstances from equivalent pa-



tient groups, and adverse events are prospectively defined and sought for in an effective manner. Such studies do not exist for the Recovery filter or its competitors. Therefore, the consultant judged that the literature is an inadequate source of reliable information upon which to make a risk/benefit assessment for the Recovery filter, either alone or in comparison to other IVC filters.

- 2) The consultant's analysis of the reports to Bard of adverse events associated with Recovery, along with competitors' information available via the MAUDE and IMS databases, showed the following:
 - a. Reports of death, filter migration (movement), IVC perforation, and filter fracture associated with Recovery filter were seen in the MAUDE database at reporting rates that were 4.6, 4.4, 4.1, and 5.3 higher, respectively, than reporting rates for all other filters. These differences were all statistically significant. Recovery's reporting rates for all adverse events, filter fracture, filter migration, and filter migration deaths were found to be significantly higher than those for other removable filters. The TrapEase filter was found to have a statistically significant increased reporting rate for IVC thrombosis when compared to reporting rates for other filters.
 - b. These reported adverse event rates were analyzed in conjunction with a bench test performed at BPV. This test measured "migration resistance" in a simulated IVC. Recovery filter had the lowest mean migration resistance (50 mm Hg), just below that of the removable Tulip filter (55 mm Hg). Linear regression analysis showed a significant inverse correlation (R^2 values of 0.40 to 0.65) of reported migration rates to the migration resistance values in the bench test.
 - c. An analysis of the quality and validity of this analytical approach (use of MAUDE and IMS databases to generate comparative event rates), however, was performed as well. Many references were found that discussed the inadvisability of using MAUDE data for this purpose. Reported event data are seriously flawed, due to underreporting, various acknowledged forms of bias (such as the known propensity for more reports of adverse events in newer products), and confounding effects (such as lack of comparability in patient groups). The FDA has stated that such an approach is "...problematic, if not completely biased" [1] and "Accumulated reports cannot be used to calculate incidence or to estimate drug risk. Comparisons between drugs cannot be made from these data." [2] Similar biases were discussed for use of the IMS sales data, in particular, the known lag period that exists between data collection and data publication, leading to large biases in data for products that are new or where indications are in evolution. Thus, actual incidence rates cannot be determined by this approach; these data are better interpreted as providing a signal for further investigation.
 - d. A risk/benefit assessment has not been done, because the potential unique benefits of the Recovery filter (e.g., in certain patient groups) have not been evaluated as part of the consultant's report.
- 3) Little formal analysis has been completed with respect to potential clinical trials to obtain more definitive risk/benefit information. A randomized, controlled trial is the gold standard for determining risks and benefits; however, such a study is likely to require many subjects and therefore be difficult or impossible to execute. The consultant stated that a survey of physicians regarding their use of IVC filters and/or an analysis of data from a large-payer or provider organization might be alternative approaches that might provide useful information in a shorter timeframe.

In addition to the consultant's report, a case-by-case analysis of all reported Recovery complaints as of December 13, 2004 related to filter migration, filter fracture, IVC thrombosis, IVC perforation and recurrent pulmonary embolus was performed.

The Actual Occurrence of Injuries: Serious injury is defined here as reported death, or necessity for a surgical intervention to prevent death or serious injury. Reported recurrent pulmonary embolus or IVC thrombosis despite the presence of the filter were also classified as serious injury. In addition, migration of a filter or filter fragments to the heart or lung, or the presence of a filter fragment outside the vasculature, were classified as serious injury, since there is a possibility that serious injury could develop in the future.

With these criteria, there were a total of 32 reported serious injuries, a reporting rate of 0.153%. Details of these reports are given below.

Human Exposure to the Problem: About 20,827 Recovery filters have been distributed as of December 13, 2004.

General Consequences: The consequences of reported adverse events associated with the Recovery IVC filter depend upon the kind of event. Filter migration to the heart, especially when the filter is encased in thrombus, has been associated with sudden death. In some cases, filter migration is associated with trapping of clot before it reaches the heart, and it continues to perform its primary function despite the migration. Filter fracture may be asymptomatic, but has been associated with fragment embolization to the heart causing syncope and/or arrhythmias. IVC perforation is also generally asymptomatic, but it can lead to serious bleeding and, if occurring in conjunction with filter limb fracture, may be associated with fragment migration outside the IVC to nearby organs.

Population Exposed to the Risk: All patients in whom a Recovery filter is placed are potentially at risk for filter-associated adverse events.

Mitigating/Predisposing Factors in the Population at Risk: Unknown.

Nature & Seriousness of the Risk: The nature of the injury is generally related to the cardiovascular system, such as pulmonary embolus, myocardial or pericardial puncture or damage, or bleeding. There was one case of renal vein thrombosis requiring dialysis, listed as a serious event because the filter migrated above the renal veins, thus potentially allowing clot in the lower IVC to propagate to the renal veins. However, it is also possible that renal vein thrombosis developed because of the underlying disease and was unrelated to the filter migration. There was one case of reported IVC thrombosis in a patient in whom recurrent pulmonary embolus was also reported. No further information about this case is available at this time.

The seriousness of the risk ranged from reports of patient death to no effects. There were 10 reports of death. One death was reported in association with recurrent PE, while the other 9 were associated with filter migration. Six (6) of these migration-associated deaths were migrations to the heart of a thrombus-encased filter. In a seventh case, only a small amount of clot was attached to the filter, but large clots were present in the pulmonary arteries. In one case, it was not known whether the filter contained clot, and in the remaining 2 cases, physicians judged the deaths to be unrelated to the filter. In the first of these 2 cases, the filter, without adherent clot, flowed out of the ventricle at autopsy. A chest X-ray taken during CPR and just prior to death did not reveal the filter in the heart, and migration to the heart may have occurred due to CPR or post mortem. In the second case, a CT scan performed minutes prior to death revealed migration to the upper IVC. In this case, an autopsy was not performed, and the physician stated that death was not related to the filter.

Likelihood of Occurrence of the Problem: The number, severity classification and type of complication (hazard) reported for the Recovery filter are summarized in Table I.

Table I. Reporting Rates for Adverse Events Associated with the Recovery Filter

Hazard type	Total	Reporting Rate	Serious Injury(as above)	Reporting Rate
Death	10(8*)	0.048%(0.038%*)	10(8*)	0.048% (0.038%*)
Migration	25	0.12%	16 (14*)	0.077% (0.067%*)
Fractures	33	0.158%	12	0.058%
Perforation	15	0.072%	1	0.005%
P. embolus	3	0.014%	3	0.014%
[IVC Thrombosis 1**		0.005%	1	0.005%]
Total	76**	0.365%	32 (30)	0.153% (0.149%)

* Number and rates if the 2 migration-associated deaths that were judged not related to the filter are excluded.

** Recurrent pulmonary embolism was also reported in this case; therefore, the total number of patients/reports is listed as 76 and not 77.

A summary of reported rates for these filter-related complications in the literature is provided in Table II.[3] These rates refer to the use of permanent, non-removable filters.

Table II. Reported Rates of IVC Filter Complications Provided by Literature Review.

Threshold levels are quality improvement guidelines published by the Society of Interventional Radiologists. Reference: Grassi CJ, Swan TL, Cardella JF et al: Quality improvement guidelines for percutaneous permanent inferior vena cava filter placement for the prevention of pulmonary embolism. J Vasc Interv Radiol 2003;14:S271-S275.

Hazard type	Reported rates	Threshold (for review)
Death	0.12%	< 1%
Filter Embolization*	2-5%	2%
Fractures	2-10%	Not listed
Perforation	0-41%	Not listed
P. embolus	0.5-0.6%	5%
IVC Occlusion**	2-30	10%

* This is equivalent to Migration in the Table above listing Recovery reporting rates

** This is equivalent to IVC Thrombosis in the Table above

Likelihood of Harm if the Problem Occurs: See above for the reporting rates of serious injury, defined as described in The Actual Occurrence of Injuries.

Is the Product Essential to Health: Yes, in selected patient groups. As mentioned above, a general consensus exists for the utility of IVC filters in high risk patient groups despite the lack of definitive RCTs.

Is there an Alternative Available: Yes. Alternative permanent and removable IVC filters exist. However, the Recovery filter is unique in the length of the implant period. The Recovery implant period is not limited in the Recovery instructions for use (IFU), and can be utilized as a permanent filter. The clinical experience for the other removable filters, as discussed in the product IFUs, reports short implant periods (mean implant period about 2-3 weeks) before filter removal must be undertaken.

Must the Problem Device be Removed or Corrected Surgically: Yes, in some cases.

Is the Problem Expected & Within an Acceptable Statistical Range: From the analysis of the MAUDE and IMS databases, Recovery reporting rates are significantly higher than those of other filters. In conjunction with these data, there appears to be a significant correlation, although R^2 values are only in the 0.5 range, of the migration reporting rates with the simulated migration resistance bench test. However, the flaws in the data collection methodologies makes calculation and comparison of actual incidence rates impossible from these data, and no definitive conclusions as to relative performance can be made. Adverse events rates reported in the literature are well above these reporting rates. But, as discussed above, direct comparisons of reporting rates to literature-derived rates are not possible because mostly permanent filters have been studied and the data have been collected using markedly different detection methods and patient populations. However, further investigation of these reported adverse events is warranted because of the size of the differences in the reporting rates and the correlation with the bench test of migration resistance.

Can the Problem be Corrected in the Field: No.

Is the Problem or Health Hazard Obvious to the User: No.

Can the Product Continue to be Used with Proper Warnings: One could consider providing summary information concerning the analysis of reporting rates to physicians in the context of the limitations of the data. Further work into the collection of survey data from surgeons or payors might be explored.

Is the Device Used Only by Specially Trained Health Care Professionals: Yes.

References:

- [1]. Goldman SA. Limitations and strengths of spontaneous reports data. Clin Ther 1998; 20 Suppl C: C40-44.
- [2]. Jones JK. Spontaneous reports cannot serve as a basis for comparison of two drugs. Am J Cardiol 2003;92:1141-1142.
- [3]. Grassi CJ, Swan TL, Cardella JF, et al: Quality improvement guidelines for percutaneous permanent inferior vena cava filter placement for the prevention of pulmonary embolism. J Vasc Interv Radiol 2003;14:S271-S275.

EXHIBIT Y

(Exhibit 2)

May 1, 1997

Dear Contact Lens Care Product Manufacturer or Interested Person:

The enclosed GUIDANCE FOR INDUSTRY--PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS represents the special control which has been determined by the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) as necessary to provide reasonable assurance of the safety and effectiveness of class II contact lens care products (listed below).

This document represents the agency's current thinking on the preparation of 510(k)s for contact lens care products. It does not create or confer any rights for or on any person, and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

The draft guidance was initially provided to the public on April 1, 1996, at which time the agency requested comments from interested persons. As discussed at the July 26, 1996, meeting of the Ophthalmic Devices Panel (Panel), FDA has evaluated the comments received and has revised the guidance document to incorporate changes resulting from comments determined to have scientific merit.

PLEASE NOTE THAT THE MAY 1, 1997, DOCUMENT REPLACES THE APRIL 1, 1996, VERSION AS THE APPROPRIATE GUIDANCE DOCUMENT THAT CONTAINS THE "SPECIAL CONTROLS" WHICH SHOULD BE FOLLOWED FOR SUBMISSION OF A 510(k). PLEASE READ THIS DOCUMENT CAREFULLY BECAUSE IT CONTAINS IMPORTANT ADDITIONS, DELETIONS, AND REVISIONS FROM THE APRIL 1, 1996, VERSION.

The Safe Medical Devices Act (SMDA) requires that the Food and Drug Administration (FDA) issue an order placing class III transitional devices in class II if FDA has not determined that the devices must remain in class III.

FDA also requires that appropriate regulatory safeguards (i.e., special controls) be in effect when reclassification occurs. The order will be published in the FEDERAL REGISTER announcing the reclassification of soft (hydrophilic) and rigid gas permeable contact lens care products and heat disinfection units. Reclassification will be effective 30 days from date of publication of the order. Devices covered by this reclassification include generic types of devices as follows:

1. Rigid Gas Permeable Contact Lens Care Products: A rigid gas permeable contact lens care product is a device intended for use in the cleaning, conditioning, rinsing, lubricating/rewetting, or storing of a rigid gas permeable contact lens. This includes all solutions and tablets used together with rigid gas permeable contact lenses.
2. Soft (Hydrophilic) Contact Lens Care Products: A soft (hydrophilic) contact lens care product is a device intended for use in the cleaning, rinsing, disinfecting, lubricating/rewetting, or storing of a soft (hydrophilic) contact lens. This includes all solutions and tablets used together with soft (hydrophilic) contact lenses and heat disinfecting units intended to disinfect a soft (hydrophilic) contact lens by means of heat.

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Specific devices covered by this reclassification include:

- Saline Solutions (including dry products/tablets)
- Cleaners (Daily Cleaners and Periodic Cleaners)
- Chemical Disinfecting Products for Contact Lenses
- Multi-Purpose Solutions
- In-Eye Contact Lens Solutions (e.g., Lubricating and/or Rewetting Drops)
- Heat Disinfecting Units

The reclassification order does not apply to such contact lens care products as contact lens cases and cleaning accessories (e.g., mechanical cleaning aids and cleaning pads) because these devices have not been separately classified.

In the near future FDA intends to revise 21 CFR 886.5918 and 886.5928 to include such care products as contact lens cases and cleaning accessories (e.g., mechanical cleaning aids and cleaning pads). For this reason, we have included guidance on submitting a 510(k) for these contact lens care products in the enclosed document.

This guidance should be used for all premarket notification submissions made after reclassification occurs. Manufacturers should be aware that although this document represents the special control required by SMDA, it is expected to be impacted by ongoing policy initiatives within CDRH and FDA's efforts to harmonize its data requirements with international standards. Any significant updates or changes in data requirements will be announced at forthcoming meetings of the Panel. Although comments received to date have been considered prior to this revision, interested persons may submit written comments at any time, which will be incorporated in future updates of this guidance if CDRH determines that they are appropriate. Comments should be submitted to:

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857

and

Division of Ophthalmic Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850

Page 3 - Contact Lens Care Product Manufacturer or Interested Person

The guidance document is available on the CDRH Worldwide web home page at "<http://www.fda.gov/cdrh>." You are encouraged to obtain electronic copies; however, if you are unable to do so, you may obtain a hard copy by faxing your request to the Division of Small Manufacturers Assistance (DSMA) [fax: (301) 443-8818].

I would like to take this opportunity to thank the Panel members, contact lens industry and other interested persons for taking the time and effort to evaluate and comment on this special controls document. In addition, I would like to thank the members of the Vitreoretinal and Extraocular Devices Branch and others who have worked extremely hard in preparing this guidance document.

Questions concerning this guidance document may be addressed to James F. Saviola, O.D., or Muriel Gelles at (301) 594-1744.

Sincerely yours

A. Ralph Rosenthal, M.D.
Director
Division of Ophthalmic Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Guidance for Industry

PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS

This document represents the agency's current thinking on the preparation of a 510(k) for contact lens care products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. The guidance is available on the Worldwide web on CDRH's home page at "<http://www.fda.gov/cdrh>."

While this guidance document represents a final document, comments and suggestions may be submitted at any time for agency consideration to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., Rm. 1-23, Rockville, MD 20857 or by writing to James F. Saviola, O.D., Chief, Vitreoretinal and Extraocular Devices Branch (HFZ-460), Division of Ophthalmic Devices, Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850. This guidance document replaces the draft PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS, which issued on April 1, 1996.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Devices and Radiological Health
May 1, 1997

PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR
CONTACT LENS CARE PRODUCTS

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I. INTRODUCTION

The Safe Medical Devices Act of 1990 (SMDA) requires that the Food and Drug Administration (FDA) issue an order placing class III transitional devices [e.g., contact lens care products such as soft (hydrophilic) and rigid gas permeable contact lens solutions (including dry products/tablets) and heat disinfection units] in class II if FDA has not determined that the transitional devices must remain in class III. The order, issued by FDA, is effective 30 days after publication in the FEDERAL REGISTER. It includes reclassification of rigid gas permeable and soft (hydrophilic) contact lens solutions (including dry products/tablets) and heat disinfection units (defined in 21 CFR 886.5918, 886.5928, and 886.5933, respectively) from class III (premarket approval) into class II (special controls). This guidance document sets forth the general information and special controls FDA believes are needed to assure the safety and effectiveness of contact lens care products such as rigid gas permeable and soft (hydrophilic) contact lens solutions (including dry products/tablets) and heat disinfection units and the evidence that demonstrates the substantial equivalence of these devices to legally marketed devices [21 CFR 807.92(a)(3)]. For purposes of this guidance document, the term "class II" is used to describe a generic type of contact lens care product. However, each manufacturer [i.e., 510(k) holder] should be aware that an unapproved individual contact lens care product is not a class II device until it has been determined to be a class II device by classification through the premarket notification (510(k)) process.

Definition of Contact Lens Care Products Covered by this Guidance Document:

- A. Class II contact lens care products are defined in 21 CFR 886.5918 and 886.5928, and generally include:
- Saline Solutions
 - Cleaners (Daily Cleaners and Periodic Cleaners)
 - Chemical Disinfecting Products for Contact Lenses (including Conditioning Solutions for Hydrophobic Lenses)
 - Multi-Purpose Solutions
 - In-Eye Contact Lens Solutions (e.g., Lubricating and/or Rewetting Drops)
 - Heat Disinfection Units
- B. Contact Lens Cases and Contact Lens Accessories (e.g., Mechanical Cleaning Aids and Accessory Cleaning Pads):

Although contact lens cases and contact lens accessories have not been separately classified as of the date of this guidance, in the past FDA has reviewed applications for these devices through the 510(k) process.

The Center for Devices and Radiological Health (CDRH) believes that it is appropriate to include guidance for submitting 510(k)s for these devices in this document. At this time the Ophthalmic Devices Panel (Panel) has recommended that contact lens cases be classified in class II; however, final classification has not occurred to date. The remaining unclassified lens care products will be brought before the Panel for classification in the near future. For this reason we have

included guidance on information that should be included in 510(k)s for these devices.

As FDA re-evaluates its data requirements for contact lens care products and works to harmonize its requirements with international standards, significant changes in our guidance may be forthcoming. Such changes may include modifications in test methods, definitions, and especially in the design of clinical trials for care products, all of which are now being considered. Any changes in requirements will be announced at forthcoming meetings of the Panel and copies will be placed on the CDRH Worldwide web (www) home page at "<http://www.fda.gov/cdrh>." You are encouraged to obtain electronic copies; however, if you are unable to do so, you may obtain a hard copy by faxing your request to the Division of Small Manufacturers Assistance (DSMA) (see list of fax and telephone numbers at end of the Introduction section).

Purpose of Document:

This document is intended to provide comprehensive directions to enable a manufacturer of a contact lens care product to submit a 510(k) that FDA believes adequately demonstrates whether the device is substantially equivalent to a legally marketed device.

This document represents the agency's current thinking on the preparation of a 510(k) for contact lens care products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. It sets forth the preclinical and clinical testing that FDA believes would be acceptable to establish substantial equivalence as required by section 513(i) and 513(f) of the act.

While use of this document to prepare preclinical and clinical protocols will not ensure investigational device exemptions (IDE) approval or 510(k) clearance, following the recommendations of this document should ensure that the necessary tests are conducted. A substantial equivalence determination for a 510(k) can be expected to follow if tests are conducted properly, data are adequately analyzed and presented, applications are submitted in accordance with applicable regulations, and the test results show that the contact lens care product is substantially equivalent to a legally-marketed contact lens care product.

Persons may choose to follow the guidance herein or may follow different data collection and preparation procedures and protocols. If a person chooses to follow different collection and preparation procedures and protocols, a person may discuss the matter in advance with CDRH to prevent the expenditure of money and effort on an activity that may later be determined to be unacceptable. If alternate procedures are used, the applicant should be prepared to demonstrate to CDRH's satisfaction that such procedures demonstrate the substantial equivalence in terms of safety and effectiveness to the predicate device.

Guidance is provided on the preclinical and clinical tests which should be used to demonstrate substantial equivalence. If clinical performance data are

needed, this guidance provides directions for obtaining an IDE [see Investigational Device Exemptions (21 CFR 812) section].

The comprehensive guidance document includes matrices and descriptions of the types of preclinical testing (e.g., manufacturing/chemistry, toxicology, and microbiology) that should be completed prior to submitting a 510(k) or, if clinical performance data are necessary to demonstrate substantial equivalence, prior to seeking IDE approval from an institutional review board (IRB). The document also includes recommended test methods for meeting these requirements.

The clinical portion of this document includes the major elements of clinical performance data collection and suggested methodologies to be included in the protocol. The clinical protocol is part of the investigational plan that must be submitted to an IRB in order to obtain approval of an IDE under 21 CFR Part 812.

Other elements of the guidance document include: (1) general information on the applicable regulations and requirements for labeling of contact lens care products, (2) requirements for modifications of a legally marketed contact lens care product (see manufacturing/chemistry, toxicology, and clinical recommendations), and (3) general information needed in a 510(k) submission.

Preclinical or clinical data in other documents on file with CDRH may be incorporated by reference into a 510(k). To be referenced, documents such as IDEs, 510(k)s, premarket approval applications (PMAs) or device master files (DMFs) should have been submitted by the applicant, or the applicant should provide CDRH with appropriate authorization from the submitter. This authorization should be in the form of a letter addressed to the Document Mail Center, HFZ-401, CDRH, 9200 Corporate Blvd., Rockville, Maryland 20850, referencing the correct document number.

The Division of Ophthalmic Devices (DOD) should be consulted if questions remain after reading this document (see list of telephone numbers at end of Introduction section).

Pertinent Regulations:

The FDA regulations especially relevant to class II contact lens care products are:

- Device Classes (section 513(a)(1) of the act)
- Establishment Registration and Device Listing for Manufacturers of Devices (21 CFR 807)
- Premarket Notification Procedures (21 CFR 807, Subpart E)
- Investigational Device Exemptions (21 CFR 812)
- Protection of Human Subjects; Informed Consent (21 CFR 50)
- Institutional Review Boards (21 CFR 56)
- Good Laboratory Practice for Nonclinical Laboratory Studies (21 CFR 58)
- Determination of Safety and Effectiveness (Defines Valid Scientific Evidence) (21 CFR 860.7)
- Good Manufacturing Practice for Medical Devices: General (21 CFR 820)

- Medical Device Reporting (21 CFR 803)
- Labeling [21 CFR 801 (see Section V, Labeling)]

Each of these regulations is briefly discussed below.

Device Classes [Section 513(a)(1) of the Act]:

Class II devices are subject to both general and special controls. General controls include the prohibition on adulteration (section 501 of the act); prohibitions on misbranding (section 502 of the act); banned devices (section 516 of the act); notification of risks and repair, replacement, or refund (section 518 of the act); records and reports (section 519 of the act); restricted devices (section 520(e) of the act), good manufacturing practices (section 520(f) of the act); registration of establishments (section 510 of the act); listing of devices (section 510(j) of the act); and submission of a premarket notification (section 510(k) of the act). Special controls may include the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines [including guidelines for the submission of clinical data in 510(k) submissions in accordance with section 510(k)], recommendations, and other appropriate actions as deemed necessary to provide reasonable assurance of the safety and effectiveness of the device.

Establishment Registration and Listing for Manufacturers of Devices (21 CFR 807):

Medical device manufacturers, initial distributors (U.S. importers), and distributors are required to register their establishments by supplying CDRH with the information required on registration form FDA 2891 (Initial Registration of Device Establishments). Manufacturers are also required to list their devices in commercial distribution in the U.S. by completing form FDA 2892 (Medical Device Listing). Foreign manufacturers may, but are not required to register; however, they must list their devices. Questions about registration and listing may be addressed to DSMA (see fax and telephone numbers at the end of the Introduction section).

Premarket Notification Procedures (21 CFR 807, Subpart E):

Most devices are cleared for commercial distribution or marketing in the U.S. through the 510(k) process. In this process, the manufacturer makes a 510(k) submission to CDRH and must receive a letter (order) from CDRH permitting commercial distribution. This order is based on CDRH's finding the device substantially equivalent to a device legally marketed in the U.S. The manufacturer must provide in the submission, among other things, evidence of such substantial equivalence. What constitutes substantial equivalence is explained in section 513(i)(1)(A) of the act. Substantial equivalence means that a device has the same intended use and the same technological characteristics (i.e., design, material, function, and other similar features) as the predicate device; or has the same intended use and new technological characteristics, but it can be demonstrated that the device is as safe and effective as the predicate device and does not raise different types of questions regarding safety and effectiveness from the predicate device.

The 510(k) notification requirement applies (21 CFR 807.81): whenever a manufacturer markets a device for the first time; when there is a change in the intended use; or whenever a legally marketed device is modified in a way

that could significantly affect its safety and effectiveness. It is not intended that a 510(k) be submitted for every change, but only where such changes could significantly affect safety or effectiveness. CDRH believes that the manufacturer is best qualified to make the initial determination, which should be based on the exercise of good judgment, adequate supporting data, and sufficient documentation in conjunction with general written policies and guidance from CDRH. The manufacturer should be aware, however, that if he or she makes a decision not to submit a new 510(k), CDRH can overrule that decision and take appropriate regulatory action. If a manufacturer does make a change or modification to the device and does not submit a 510(k), he or she should document the reason for not submitting a 510(k) in the good manufacturing practice (GMP) device master record and make it available to FDA upon request.

Subpart E of 21 CFR 807.81 (Premarket Notification Procedures) provides guidance on the type of changes for which an applicant must submit a 510(k) if the change could significantly affect the safety and effectiveness of the device. Additionally, you should contact DSMA (see fax and telephone numbers at the end of the Introduction section) to obtain a copy of the most recent CDRH general guidance on changes to an existing device that may require submission of a new 510(k). Manufacturers should be aware, however, that a device specific guidance document such as the "GUIDANCE FOR INDUSTRY--PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS" supersedes or provides additional guidance to a CDRH general guidance involving device modifications that may require submission of a new 510(k). If, after attempting to evaluate the change, manufacturers are still uncertain about the need for a 510(k), they may write a letter explaining the changes in detail, referencing the 510(k) number, and mail it to the Document Mail Center, CDRH (address above).

Once a 510(k) has been submitted, additional information may be requested by CDRH, in which case the 510(k) application will be placed on hold. A letter is issued stating that the file will be retained for 30 days while waiting for the submitter's response. If a response is not received within 30 days, the 510(k) may be deleted. The submitter should respond within 30 days or, if the 30-day period cannot be met, request an extension by letter to the Document Mail Center, CDRH (address above), referencing the 510(k) number. When CDRH receives the additional information, the review period begins again. This happens each time additional information is requested.

Premarket notification review allows CDRH to find not substantially equivalent (NSE) devices that: (a) present new types of questions of safety and/or effectiveness relative to the predicate devices; (b) appear to perform less safely or effectively than legally marketed devices; and (c) have indications that are a new intended use.

If CDRH determines that a device is NSE, the manufacturer may appeal the NSE decision, file a reclassification petition, or submit a PMA. When a manufacturer and CDRH disagree about the NSE decision for a device, the following applies:

- A 510(k) that is determined to be NSE is automatically classified into class III, and unless reclassified into class I or II, is subject to premarket approval. The manufacturer may request

reconsideration of an NSE decision. The 510(k) Staff may be contacted for information on how to request reconsideration of an NSE decision (telephone number at end of the Introduction section).

- Under section 513(f) of the act, a manufacturer of a class III device may petition CDRH for reclassification of this device into class I or class II. CDRH will refer a petition to the appropriate FDA advisory panel for review and recommendation. The content and format requirements of a reclassification petition are in 21 CFR 860.123.
- If determined to be NSE because of lack of performance data, the manufacturer may resubmit another 510(k) with additional data.

A 510(k) should be dated, and list the applicant's (submitter's) name, address, contact person (if different from applicant), telephone number, and must be signed by the applicant. The 510(k) should contain a table of contents, be submitted in duplicate on standard sized paper with pages numbered, securely bound (if necessary), and three-hole punched. The manufacturer should designate in the cover letter that the submission is a "510(k) notification." All attachments to the 510(k) submission should be appropriately identified. The general information section should include:

- the trade name (proprietary name) for the device;
- the identification of the predicate or legally marketed device to which substantial equivalence is being claimed;
- the common name or the classification name (21 CFR 807.87) of the device;
- a description of the device that is the subject of the 510(k);
- a statement of the intended use of the device;
- a statement of how the technological characteristics of the device compare to those of the predicate device;
- the establishment registration number [although not required in a 510(k), the applicant will need to register his or her establishment within 30 days of product release];
- the address of the manufacturing facility/facilities, including the sterilization site(s);
- the class in which the device has been placed (class I, II, or III) under section 513 of the act, and, its appropriate panel, if known (if the submitter determines that the device has not been classified, a statement of that determination and the basis for that determination);
- the reason for the premarket notification [e.g., a new device or a modification to an existing device (if the 510(k) is for a modification, describe in detail the reason for the modification and provide the equivalent device's 510(k) number)];

- compliance with the requirements of the act under section 513 special controls (class II devices);
- copies of draft labeling and available advertising for the device;
- engineering drawings (for care products such as heat disinfection units, lens cases, etc.);
- under 21 CFR 807.92 and 807.93 the 510(k) submitter must include either a summary of the safety and effectiveness information upon which the substantial equivalence determination is based, or a statement in the 510(k) that the submitter will make available the safety and effectiveness information to interested persons upon request. If a statement is provided, it should be (1) dated (2) signed by the certifier, (3) made on a separate page of the premarket notification submission, and (4) clearly identified as "510(k) statement" which contains the following:

"I certify that, in my capacity as [The Position Held In Company by Person Required To Submit The Premarket Notification, Preferably The Official Correspondent In the Firm], of [Company Name], I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness information, but excluding all patient identifiers, and trade secret and confidential commercial information, as defined in 21 CFR 20.61."
- a dated and signed statement certifying that the submitter believes, to the best of his or her knowledge, that all data and information submitted in the premarket notification are truthful and accurate, and that no material fact has been omitted in accordance with 21 CFR 807.87(j).

Subpart E of Section 807 of 21 CFR and the booklet "Premarket Notification 510(k): Regulatory Requirements for Medical Devices" (HHS Publication FDA 92-4158) provide detailed explanations and examples of ways that companies can comply with the 510(k) requirements. DSMA can provide you with the regulation and this booklet, answer questions, and provide guidance regarding the regulatory process. DSMA's fax and telephone numbers are listed at the end of the Introduction section.

Investigational Device Exemptions (21 CFR 812):

Data from clinical testing may be necessary to demonstrate the substantial equivalence of a contact lens care product to a legally marketed device. To collect these clinical data, an approved IDE is required before the sponsor (usually the manufacturer) can distribute investigational medical devices for clinical testing. The IDE regulation describes procedures for obtaining an

approved IDE and outlines the responsibilities of a sponsor and an investigator during a clinical investigation with a medical device.

FDA considers clinical studies of certain solutions intended to be used directly in the eye to be significant risk investigations which require both IRB and FDA review and approval prior to initiating clinical studies. Examples of significant risk investigations include studies of: (1) solutions containing new types of active ingredients that have no history of ophthalmic use and cannot be adequately characterized from a safety standpoint by the preclinical testing contained in this guidance, or (2) solutions containing biologic or pharmaceutical ingredients that could present a risk to the health and safety of the subjects, and would involve overlapping jurisdiction with other Centers within FDA.

FDA considers most clinical studies of contact lens care products to be non-significant risk investigations since the active ingredients can be adequately characterized from a safety standpoint by the preclinical testing contained in this guidance. The abbreviated requirements of the IDE regulation [21 CFR 812.2(b)] apply for non-significant risk investigations, which basically require the following:

1. The sponsor must submit and obtain approval for a non-significant risk device study from a properly constituted IRB (21 CFR 56), or FDA if no IRB exists (21 CFR 812.62(b)), prior to distributing devices for a clinical investigation (21 CFR 812.30).
2. All test subjects must give their informed consent (21 CFR 50) before being treated with the investigational device. Informed consent is obtained on a written form advising the subjects of their rights as voluntary research subjects, apprising subjects of risks, benefits, and alternate procedures, if any, and test procedures involved.
3. All investigations must be properly monitored.
4. Certain recordkeeping and reporting requirements must be met [see 21 CFR 812.2(b)(1)(v)-(vi)].

FDA review and approval is not required for an investigation of a non-significant risk device. A sponsor needs to obtain IRB approval and follow the requirements of 21 CFR 812.2(b)(1)(i) through (vii).

Under the abbreviated requirements for non-significant risk device clinical studies (21 CFR 812.2(b)), an IRB must determine that a particular contact lens care product poses a non-significant risk. For a device investigation to be determined to be non-significant risk, a sponsor must provide an IRB with a statement of why the investigation does not pose a significant risk, and the IRB must agree with this assessment. The IRB must also approve the investigation as a non-significant risk study.

IRBs should be provided with all information necessary to reach a sound decision. This information, in the case of a contact lens care product, should include informed consent forms and the clinical protocol. It is important to note that, in the case of non-significant risk investigations, although preclinical data are not required to be submitted to CDRH until a 510(k) is submitted, the sponsor should conduct preclinical tests prior to

initiating a clinical study to predict product performance and to protect the health of the subjects. The purpose of preclinical tests is to evaluate whether subjects will be at undue risk, and thus preclinical test results should be submitted to the IRB for its review prior to testing in humans.

IDE Study Design:

Sponsors of investigations should consider carefully how to adequately demonstrate the substantial equivalence of their specific devices to legally marketed devices and design their study to assure that the data provide valid scientific evidence, as defined in 21 CFR 860.7; to answer all clinical objectives properly; and to form a sound basis to support the intended use and claim(s) being made in the labeling.

Manufacturers should carefully review the clinical recommendations in this guidance document, which have been designed to assist in developing adequate clinical protocols. In addition, they should consult with the DOD scientific staff, if necessary, when preparing their clinical protocol. The preparation of an adequate protocol is one of the most important aspects of the clinical investigation and essential for a successful 510(k) when clinical performance data are required to demonstrate substantial equivalence. The protocol should be designed to fully support the proposed labeling claim(s) and intended use of the device. The sponsor is responsible for ensuring that the study design is appropriate and that all necessary tests are completed. If alternative tests are more appropriate than those listed or additional tests must be conducted, the overall design of the study and its justification are the responsibility of the study sponsor.

Information available to sponsors includes the IDE regulation (21 CFR 812) and related information. Please contact the IDE Staff or DOD for further guidance (see telephone numbers at the end of the Introduction section).

Protection of Human Subjects; Informed Consent (21 CFR 50):

The fundamental purposes of IRB review and of informed consent are to assure that the rights, safety, and welfare of subjects are protected. A signed informed consent form is evidence that the information required by section 50.25 has been provided to a prospective investigational subject. IRB review of the form to ensure that the subject is given adequate information concerning the study serves a dual function: protection of the subject and documentation that the institution complied with applicable regulations. Informed consent must be obtained in accordance with the informed consent regulation, and any informed consent form used must embody the elements of informed consent required by 21 CFR 50.25. The consent form itself is an aid to ensure that adequate information is provided to the subject. The signed consent form provides documentation of a subject's consent to participate in a study. The entire informed consent process involves giving a subject information concerning the study, providing adequate opportunity for the subject to consider all options, responding to the subject's questions, ensuring that the subject has comprehended this information, and, finally, obtaining the subject's voluntary consent to participate. Informed consent must be documented pursuant to 21 CFR 50.27 and is required by 21 CFR 50.20 for all subjects in clinical investigations of medical devices. Specific questions may be addressed to the IDE Staff (see telephone number at the end of the Introduction section).

Institutional Review Boards (21 CFR 56):

An IRB is a board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct continuing review of biomedical research involving human subjects in accordance with FDA regulation. The purpose of IRB review is to assure that:

- risks to subjects are minimized, and are reasonable in relation to anticipated benefits;
- selection of subjects is equitable;
- informed consent will be sought from each prospective subject or the subject's legally authorized representative and will be documented;
- where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects; and
- there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

The IRB regulation outlines membership and review requirements. All IRBs must conform to and comply with all requirements in this regulation.

Specific questions may be addressed to the IDE Staff (see telephone number at the end of the Introduction section).

Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies (21 CFR 58):

The purpose of this regulation is to assure the high quality of nonclinical laboratory testing required to evaluate the safety of medical devices. Sponsors should state in all submissions whether or not nonclinical laboratory tests were conducted in accordance with this regulation. When procedures are not conducted in accordance with the GLP regulation, justifications should be provided.

Specific questions may be addressed to the IDE Staff (see telephone number at the end of the Introduction section).

Determination of Safety and Effectiveness (Defines Valid Scientific Evidence) (21 CFR 860.7):

This regulation defines what does and does not constitute valid scientific evidence for the purpose of determination by FDA that there is reasonable assurance that a device is safe and effective for its intended use. Although a 510(k) only requires a demonstration of substantial equivalence to a legally marketed device, this demonstration is in terms of the device being as safe and as effective as a legally marketed device and that the device does not raise different types of questions of safety and effectiveness than the predicate device.

Specific questions about the interpretation of this regulation should be addressed to DOD (see telephone number at the end of the Introduction section).

Good Manufacturing Practice for Medical Devices: General (21 CFR 820):

The Good Manufacturing Practice (GMP) for Medical Devices General Regulation, required by section 520(f) of the act, covers the methods used in, and the facilities and controls used for, the design, manufacture, packaging, storage, and installation of devices. It covers the following general areas: organization and personnel; buildings; equipment; controls for components, processes, packaging, and labeling; device holding, distribution, and installation; device evaluation; device and manufacturing records; complaint processing; and quality assurance (QA) system audits.

SMDA amends section 520(f) of the act to authorize the inclusion of preproduction design validation in the GMP regulation. A revised GMP regulation was published in the FEDERAL REGISTER on October 7, 1996 [61 FR 52601] that incorporates preproduction design controls.

Specific questions on GMP requirements may be addressed to DSMA (see fax and telephone numbers at the end of the Introduction section).

Medical Device Reporting (21 CFR 803):

The Medical Device Reporting (MDR) regulation requires all manufacturers of medical devices to report to FDA within 30 days whenever the firms receive or otherwise become aware of information that reasonably suggests that one of their marketed devices: (1) may have caused or contributed to a death or serious injury; or (2) has malfunctioned and that the device or any other similar device would be likely to cause or contribute to a death or serious injury if the malfunction were to reoccur.

Manufacturers and importers of devices are required to establish and maintain an MDR file and to permit any authorized FDA employee at reasonable times to have access to, and to copy and verify the records contained in this file. FDA considers any expression of dissatisfaction, be it oral or written, regarding identity, quality, durability, reliability, safety, effectiveness, or performance of a device, to be a complaint. However, not all complaints meet the MDR reporting criteria.

Copies of the MDR regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by contacting DSMA (see fax and telephone numbers at the end of the Introduction section).

Management Initiatives:

On June 30, 1993, new policies to improve the device approval process were announced by CDRH. These new policies are as follows:

- **Expedited review:** To assure that those devices which represent major advancements in medical care reach the market without delay, CDRH has put into effect a "fast track" review system for them. These device applications will be placed in a separate queue and not treated under the usual "first-in, first-reviewed" policy. Included in the expedited review category will be devices used to treat serious conditions for which no alternative treatments exist and devices that offer decidedly greater clinical benefits or lower risks than existing technologies.

- **Refuse-to-accept policy:** In the past, inadequate and incomplete applications wasted a great deal of CDRH's time. Reviewers were obliged to "re-cycle" these applications, going back to the company repeatedly to request needed information or to clarify poorly presented data. To address this problem, the agency has established a "refuse-to-accept" policy that will specify the minimum criteria for accepting an application. If these are not met, the application will be rejected.

Some specific reasons to refuse to accept a 510(k) submission for contact lens care products would be failure to include information establishing substantial equivalence, a 510(k) summary of safety and effectiveness or 510(k) statement, or a truth and accuracy statement.

- **Setting review priorities using risk assessment (previously called "Triage"):** Early in the review process, CDRH will determine the potential health hazard posed by each device and will focus most of its attention on those devices that pose a significant risk to patients. Devices with minimal risk potential will receive a less extensive review.

To achieve this, three review tiers have been identified: Tier I - Essentially a focused labeling review for intended use/indications for use; Tier II - Routine scientific and labeling review (the majority of 510(k)s will be in this tier); and Tier III - Intensive scientific and labeling review, using a team review approach, for all first and second of a kind devices utilizing new technology or having new intended use(s), as well as other devices determined by their inherent risk to require an intensive review.

Contact lens care products, including solutions that incorporate traditional preservative systems and intended uses, are currently assigned to a Tier II review.

- **Status reports to manufacturers:** In the past, device manufacturers have often not been able to determine the status of their 510(k) submissions as they proceed through the review system. This has proven a major source of frustration, particularly since lack of information can interfere with sound business planning. To address this problem, CDRH has established a computerized system through which manufacturers will receive a status report on their 510(k) submissions within 3 days of requesting it, if the application has been under review over 90 days.

More information is available on each of these policies in ODE Blue Book memos available by contacting DSMA (see fax and telephone numbers at the end of the Introduction section).

Special Controls:

This guidance document sets forth the special controls which have been determined at this time by CDRH to be necessary to provide reasonable assurance of the safety and effectiveness of class II contact lens care

products in the absence of an applicable standard. These special controls consist of the recommended protocols for the preclinical and clinical data that FDA believes establish substantial equivalence under section 513 of the act and identify modifications to contact lens products that FDA believes would require submission of a new 510(k) and labeling guidance.

CDRH has carefully considered these recommendations, but also recognizes that it is important to be open-minded about new tests which can be, and are, suggested. If different procedures are chosen by the applicant, a full justification should be submitted. The justification should clearly explain how the alternative procedure can provide the valid scientific evidence needed to demonstrate substantial equivalence. The absence of any justification and supporting evidence may mean that the application will be found unacceptable during scientific review.

DOD may be consulted prior to the initiation of any tests if, after reading the guidance document, questions remain concerning a specific test recommendation for a contact lens care product (telephone number listed below).

Fax and Telephone References:

DSMA: Fax: (301) 443-8818 (For copy of guidance document, refer to shelf number 674)

Telephone: (800) 638-2041 or (301) 443-6597

DOD: Fax: (301) 480-4201

Telephone: (301) 594-1744

IDE Staff: Telephone: (301) 594-1190

510(k) Staff: Telephone: (301) 594-1190

II. GENERAL MANUFACTURING INFORMATION

This section of the guidance contains the general manufacturing information that should be submitted in a 510(k) for contact lens solutions and tablets. For purposes of this guidance, we have focused primarily on active ingredients. However, manufacturers should also assess the effects of inactive ingredients (e.g., buffering agents and tablet coatings) on such factors as pH, tonicity, solution compatibility, enzymatic activity, preservative effectiveness, disinfection efficacy, preservative uptake/release, and critical micelle concentration of surfactant.

In 510(k) submissions, applicants should provide the general information listed below as well as the information in Section III (Product Specific Guidance), Section V (Labeling), and other applicable sections of the guidance. Applicants are reminded that when test data are submitted, complete reports of the tests as well as summary information should be included in the 510(k).

A. General Manufacturing Information for Contact Lens Solutions and Tablets:

The applicant should document and summarize the following manufacturing/chemistry information:

1. Chemical Composition of the Contact Lens Solution or Tablet:

The chemical composition of the contact lens solution or tablet should include all active and inactive ingredients and their functions.

Note: For purposes of this guidance:

- An "active ingredient" is generally defined as any chemical component that is included in the formulation of a contact lens solution or tablet in sufficient concentration to achieve the intended purpose of the specific product (e.g., a surfactant for a daily cleaner, an anti-microbial agent for a disinfecting product, an enzyme for an enzymatic tablet or a preservative for preserved lens care products).
- An "inactive ingredient" is generally defined as any chemical component other than an active ingredient (e.g., buffering agents and water) that is included in the formulation.

If the components meet United States Pharmacopoeia (USP), National Formulary (NF), or American Chemical Society (ACS) specifications, this should be noted. If sorbic acid is used as a component, aldehyde should be quantified and its specification justified. For any non-compendial component, the applicant should establish approved raw material specifications in accordance with GMPs and submit them in the 510(k) (e.g., characterization data on this component and/or analytical results from manufacturing batches used for preclinical and clinical tests).

When applicable, a side-by-side comparison of the composition of the new device compared to the predicate device should be provided. If the new solution or tablet is identical to the predicate device in terms of concentrations of active and inactive ingredients, the general manufacturing information can be limited to a description of the manufacturing process with a flow chart, demonstration of product sterility and sterilization validation, shelf-life data, and a description of the packaging, including tamper resistant features. If the new solution or tablet is not identical to the predicate device in terms of concentrations of active and inactive ingredients, all general manufacturing information outlined below should be addressed in the 510(k). Whenever new claims are made for a marketed device, supporting information should be provided.

2. A brief description, including a flow chart, of the manufacturing process should be provided.
3. Sterility: In accordance with 21 CFR 800.10, all contact lens solutions should be sterile. Sterility should be demonstrated using USP <71>, Sterility Tests, or by an equivalently validated sterility test method. Product sterility or validated package integrity testing should be performed to support the shelf-life requested in the 510(k). [Section VI.E (Shelf-Life Protocol)].

For general information and references dealing with the development and validation of sterilization cycles, manufacturers should refer to USP <1211>, Sterilization and Sterility Assurance/General Information. Manufacturers should validate their product sterilization system(s) and cycle(s) using a suitable validation method and demonstrate the efficacy and compatibility with the product and/or container. Manufacturers should use the most recent edition and include reference(s) for the validation method in the 510(k). Some additional references on sterilization validation methods are provided below:

- ANSI/AAMI/ISO 11134: Sterilization of health care products - Requirements for validation and routine control - Industrial moist heat sterilization.
- ANSI/AAMI/ISO 11135: Medical devices - Validation and routine control of ethylene oxide sterilization.
- ANSI/AAMI/ISO 11137: Sterilization of health care products - Requirements for validation and routine control - Radiation sterilization.
- ISO/TR 13409: Sterilization of health care products - Radiation sterilization - Substantiation of 25 kGy as a sterilization dose for small or infrequent production batches.
- Validation of Aseptic Filling for Solution Drug Products. Technical Monograph No. 2. Parenteral Drug Association.

- Guideline on Sterile Drug Products Produced by Aseptic Processing June 1991. Prepared by: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Office of Regulatory Affairs, FDA.
- USP <1211> Sterilization and Sterility Assurance of Compendial Articles: Aseptic Processing.

In accordance with the Office of Device Evaluation (ODE) 510(k) Blue Book Memorandum #90-1 dated February 12, 1990, the applicant should provide the following information in the 510(k) submission to support validation of a traditional sterilizing system [e.g., steam under pressure, ethylene oxide (ETO), gamma radiation or aseptic fill process]:

- a. the sterilization method that will be used;
- b. a description of the method that will be used to validate the sterilization cycle, but not the validation data itself;
- c. the sterility assurance level (SAL) which the manufacturer will meet;
- d. a description of the packaging to maintain the device's sterility (this should not include the package integrity testing data);
- e. if sterilization involves ETO, the maximum levels of residues of ETO, ethylene chlorhydrin, and ethylene glycol which remain on the device or components of the device (e.g., bottles or container closure system); and
- f. the radiation dose, if radiation sterilization will be used.

Applicants should provide, in the 510(k), a description of the quality assurance procedures and sterility test methods used to provide routine sterility assurance.

4. Microbial Limits Test: Manufacturers of nonsterile contact lens products marketed in dry or tableted formulation should submit data from USP microbial limits testing to demonstrate acceptable microbiological quality, when applicable. These data may be omitted if the manufacturer provides data demonstrating that the level of the active ingredient concentration is inhibitory.
5. In accordance with 21 CFR 800.10(b), contact lens solutions packaged in multi-dose containers should be formulated and packaged as to volume and type of container and appropriately labeled to afford adequate protection and minimize the hazard of injury resulting from contamination during use (e.g., preserved multi-dose solutions, unit-dose containers, discard time periods).
6. Preservative Effectiveness: Manufacturers of preserved solutions should demonstrate preservative effectiveness initially and at the shelf-life requested in the 510(k). See Section VI (Recommended Test Methods) Micro--Appendix A, for guidance on the recommended

preservative effectiveness test with microbial rechallenge on day 14.

7. Shelf-Life (Stability) Data Including Product Specifications, Container and Container Sizes:

Please refer to Section VI E. (Shelf-Life Protocol) for guidance on establishing, or extension of, shelf-life.

8. Tamper Resistant Packaging: All solutions and tablets must meet the requirements of 21 CFR 800.12, Contact Lens Solutions and Tablets; Tamper-Resistant Packaging.

9. Solution Compatibility Under Recommended Care Regimen: Compatibility of the solution with the lens type (hydrophilic or hydrophobic) indicated for the product specific use should be assessed. For guidance, see applicable testing matrix and Section VI (Recommended Test Methods) Chem--Appendix C.

10. Preservative Uptake/Release: Preservative uptake/release data should generally be submitted in a 510(k) for a solution containing new preservatives for contact lens use. When applicable, manufacturers should assess the effects of inactive ingredients (e.g., buffering agents, etc.) on preservative uptake/release. However, a manufacturer may justify omission of these data in a 510(k) provided:

- a. the manufacturer demonstrates that the proposed preservative system is essentially identical in terms of chemical composition and intended use (hydrophilic lenses or rigid gas permeable lenses) to the preservative system of the predicate device; and
- b. the manufacturer demonstrates that the new preservative does not raise toxicological concerns and the new preservative carries no charge or the same charge as the lens material (e.g., generally negatively charged).

CDRH considers hydrophilic contact lenses to represent a worst case. Therefore, manufacturers who already have SE clearance for a contact lens care product intended for use with hydrophilic contact lenses do not need, unless otherwise notified, to submit additional preservative uptake/release data for adding use with hydrophobic lenses to labeling.

For guidance, see applicable testing matrix and Section VI (Recommended Test Methods) Chem--Appendix A, if the above criteria cannot be met.

B. Other Contact Lens Care Products:

Other contact lens care products included in this guidance include heat disinfecting units, lens cases, and contact lens accessories (e.g., mechanical cleaning aids and accessory cleaning pads). See Section III (Product Specific Guidance) and Section V (Labeling) for guidance on these devices.

III. PRODUCT SPECIFIC GUIDANCE

This section is a composite of mini-guidances (hereafter referred to as product specific guidance) for each of the devices included in the GUIDANCE FOR INDUSTRY--PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS. Each product specific guidance contains its own testing matrix (when applicable) to provide applicants with a summary chart and narrative explanation of preclinical and clinical testing recommendations for collecting performance data. CDRH expects that these data either be submitted or that the testing areas be addressed in the 510(k), unless the applicant provides a justification for why the data are not applicable.

The product specific matrices also apply when a marketed product is changed in a way that could significantly affect its safety or effectiveness [e.g., change or modification in the active ingredient(s)]. Applicants are reminded that when performance data are submitted in a 510(k), data should include full reports, where applicable, of the test data as well as summary information.

Please note that the information and data elements included in the General Manufacturing Information section are not repeated in each product specific guidance section, but are included by reference. In addition, Section V (Labeling) includes both general and product specific labeling guidance.

Product specific guidances included in this section are:

1. Saline Solutions
2. Cleaners (Daily Cleaners and Periodic Cleaners)
3. Chemical Disinfecting Products for Contact Lenses (e.g., chemical disinfecting solutions, chemical disinfection systems, and conditioning solutions).
4. Multi-Purpose Solutions
5. In-Eye Contact Lens Solutions (e.g., Lubricating and/or Rewetting Drops)
6. Heat Disinfecting Units
7. Contact Lens Cases
8. Contact Lens Solution Accessories (e.g., Mechanical Cleaning Aids and Accessory Cleaning Pads)

The following matrices (including preclinical and clinical guidance) and Section V (Labeling) set forth the special controls determined by CDRH to be necessary to assure the continued safety and effectiveness of the devices and the information that should be provided in a 510(k).

The applicant should compare product active ingredient(s) with those of the predicate device and refer to the appropriate section of the applicable matrix for guidance.

A. SALINE SOLUTIONS

A saline solution is generally defined as a contact lens care product (e.g., solution, capsule or tablet) containing sodium chloride as the principal active ingredient in an aqueous based solution formulation to produce a physiologically balanced saline solution (approximately 0.9% by weight). These products are either pre-formulated sterile solutions or packaged as salt tablets or capsules which require distilled water as a diluent to produce a non-sterile "homemade" saline solution. They are intended to be used with soft or rigid gas permeable contact lenses for one or more of the following:

- rinsing after cleaning to remove loosened debris and cleaning solution
- rinsing prior to lens insertion
- keeping lenses wet during heat disinfection
- storage after disinfection
- a diluent for dissolving lens care tablets (e.g., enzyme or disinfecting tablets)
- a diluent for use in hydrogen peroxide disinfection systems (limited use)

Pre-formulated sterile saline solutions can be marketed in formulations that are preserved or unpreserved; buffered or unbuffered. These solutions can be packaged in various containers (e.g., aerosols, non-aerosol, unit-dose or multi-dose).

TESTING MATRIX FOR SALINE SOLUTIONS

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	FOOTNOTE A	FOOTNOTE A	FOOTNOTE A	X
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge or Bacteriostasis for Unpreserved Products	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study				60 subj/1 mo

FOOTNOTE A: If the saline solution has a pH of 7.2 ± 0.2 and tonicity of 290-320 mOsm/kg, manufacturers do not need, unless otherwise notified, to submit solution compatibility data.

Pre-formulated Saline Solutions:

Manufacturing/Chemistry:

Pre-formulated Sterile Saline Solutions: Pre-formulated sterile saline solutions are generally maintained in the comfort range (e.g., pH = 6.6-7.8 and tonicity of 290-320 mOsm/kg) to avoid eye irritation when used in accordance with the recommended lens care regimen. In addition to the information listed in the General Manufacturing Information section and in the matrix, the following information should be provided:

1. Heat Disinfection: If the saline solution is indicated for use during heat disinfection, the effect of heat disinfection on pH, tonicity, and preservative concentration should be assessed and data submitted.
2. Diluent for Lens Care Tablets: If the saline solution is indicated for use as a diluent for enzyme tablets, tablet disintegration time and enzymatic activity time profile as indicated in labeling should be assessed, compared to a control (e.g., approved diluent), and data submitted.

Microbiology:

This section, Section II (General Manufacturing Information) and the matrix include microbiological guidance for all pre-formulated saline solutions.

1. Preservative Effectiveness: Applicants should refer to the preservative effectiveness portion of Section II (General Manufacturing Information) and Section VI (Recommended Test Methods) Micro--Appendix A for guidance. In addition, applicants should be aware that passing preservative effectiveness test with rechallenge on day 14 allows manufacturers to label preserved saline solutions for lens storage up to 30 days following disinfection. Labeling instructions for 30-day storage in preserved saline should include instructions for lens case care and the need to re-disinfect lenses after the recommended storage time.

Manufacturers submitting 510(k)s for salines preserved with sorbic acid or sorbate-based preservatives may omit the microbial rechallenge in preservative effectiveness testing. However, testing should continue as directed by the protocol in Section VI (Recommended Test Methods) Micro--Appendix A for 28 days, including enumeration of surviving microorganisms at 21 and 28 days. In order to support labeling claims for long-term storage of lenses following heat disinfection (up to 30 days), the 510(k) should include data demonstrating that passing preservative effectiveness test results were obtained using a rechallenge on day 14.

2. Multi-dose saline products may contain bacteriostatic agents (e.g., boric acid or borate) instead of traditional preservatives. In lieu of a preservative effectiveness test, a bacteriostasis

test may be conducted and the product labeled with the appropriate discard date [see Section VI (Recommended Test Methods) Micro--Appendix C].

Toxicology:

See Testing Matrix for Saline Solution and Section VI (Recommended Test Methods) Tox--Appendices A-B, for guidance on recommended tests for including in a 510(k).

Clinical:

Clinical data are not generally required to be submitted in a 510(k) for saline solutions provided the saline solution is formulated, packaged and labeled in an equivalent manner to the predicate device.

Homemade Saline Solutions (Salt Tablets/Capsules System):

A homemade saline solution is made from a salt tablets/capsules system that generally consists of salt tablets or capsules containing Sodium Chloride USP and a plastic mixing bottle of a specified size. The system is packaged with labeling instructions to use over-the-counter (OTC) distilled water as a diluent for dissolving the salt tablet or crystals. The prepared saline solution is used with soft (hydrophilic) contact lenses for rinsing PRIOR to heat disinfection and in the lens case for keeping lenses hydrated during heat disinfection. See Section V (Labeling) for guidance on recommended indications for use statements and warnings.

Chemistry:

Sodium Chloride USP or equivalent is recommended for use in manufacturing salt tablets or capsules.

Microbiology:

Microbiology testing data are generally not required to be submitted when a salt tablet or capsule system is formulated using Sodium Chloride USP, packaged and labeled in an equivalent manner to the predicate device. Microbial issues are addressed in Section V (Labeling).

Toxicology:

See Section VI (Recommended Testing Methods, Toxicology Testing for Containers) Tox--Appendix A, for guidance on recommended tests for including in the 510(k) for the container/closure system for salt tablets/capsules systems. Toxicology information is generally not required to be submitted for salt tablets or capsules formulated using Sodium Chloride USP.

Clinical:

In the early 1980s, the Ophthalmic Devices Panel recommended and CDRH concurred, that the unit-dose aspect of the salt tablets/capsules system is such that clinical testing to establish the safety and effectiveness of the product would not be needed if the salt tablets/capsules system is formulated using Sodium Chloride USP, packaged and labeled in an equivalent manner to the predicate device.

B. CLEANERS

Daily Cleaners:

A daily cleaner is generally defined as a contact lens care product containing one or more active ingredients in sufficient concentrations to loosen and remove loosely held lens deposits and other contaminants on the surface of contact lenses. A daily cleaner may also be indicated for use as a component of a lens care disinfection regimen, or as a labeled intended use for a multi-purpose lens care solution.

Daily cleaners are generally marketed as pre-formulated solutions and labeled for use in conjunction with digital manipulation (e.g., fingers) or an accessory device (e.g., mechanical cleaning aids) for a specific period of time to accomplish the intended purpose. Sufficient data should be submitted in the 510(k) to support the effectiveness of the daily cleaner when used for the minimum time period recommended in the labeling.

TESTING MATRIX FOR DAILY CLEANERS

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	X	X	X	X
Cleaning Effectiveness - Critical Micelle Concentration	X	X	X	X
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge	X	X	X	X
Microbial Limits Test (Dry Products/Tablets Only)	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study		FOOTNOTE A	FOOTNOTE B	60 subj/3 mo

FOOTNOTE A: Clinical performance data may need to be submitted depending on the physical/chemical, microbiological and toxicological data collected (i.e., a higher concentration of the active cleaning ingredient in a multi-purpose solution with a daily cleaning claim may require submission of clinical data while an increase in concentration of the active ingredient in a daily cleaner may not). If necessary, a 30 subject/1 month clinical study should be conducted.

FOOTNOTE B: If active ingredient is a surfactant, sponsor may use either appropriate in vitro tests or conduct a clinical test with 60 subject/3 months to establish the efficacy of the lower concentration of active ingredient.

Chemistry:

The following chemistry tests are applicable to a daily cleaner containing a surfactant(s) as the active ingredient. Manufacturers of daily cleaners containing active ingredients other than surfactants may wish to consult DOD before initiating test protocols. The information included in Section II (General Manufacturing Information), the testing matrix, and listed below should be provided in the 510(k):

1. Surface Tension of the Solution: [See Section VI (Recommended Test Methods) Chem--Appendix B, for recommended methodology].
2. Micelle Concentration of the Surfactant in the Solution: [See Section VI (Recommended Test Methods) Chem--Appendix B for recommended methodology].
3. Other scientifically valid method: Supporting literature and/or method validations testing information should be provided.

Microbiology:

See Testing Matrix for Daily Cleaners, Section II (General Manufacturing Information), and Section VI (Recommended Test Methods) Micro--Appendix A, for guidance on recommended tests for including in a 510(k).

Toxicology:

See Testing Matrix for Daily Cleaners, and Section VI (Recommended Test Methods) Tox--Appendices A-B, for guidance on recommended tests for including in a 510(k).

Clinical:

See Testing Matrix for Daily Cleaners for guidance on size and scope of a clinical trial. Further clinical guidance on protocol development is available in Section VI (Recommended Test Methods) Clin--Appendices A-E.

In the absence of validated in-vitro data, applicants are advised that for cleaning studies (e.g., studies of non-surfactant agents) a cross-over design with additional in-vitro analysis of worn lenses is an example of one method to demonstrate substantial equivalence to the predicate device. Sponsors may choose to consult with DOD prior to developing their protocols.

Periodic Cleaners:

A periodic cleaner is generally defined as a contact lens care product (e.g., solution or tablet) containing one or more active ingredients (e.g., enzymes) in sufficient concentrations to loosen and remove deposits (e.g., proteins) from the lens surface and from within the polymer matrix. Periodic cleaners are recommended for removing lens deposits such as proteins or lipids that cannot generally be removed from lenses with the use of a daily cleaner. Periodic cleaners have traditionally been recommended for use on a weekly basis.

Periodic cleaners are generally marketed as pre-formulated solutions or as tablets containing the active ingredients. Labeling directions for the original enzyme preparations derived from pancreatin and papain stated that lenses should be soaked for a specified time period after the enzyme tablets are dissolved in diluents such as saline solutions, chemical disinfection solutions or multi-purpose solutions to release the active ingredients.

Later technological innovations of bacterial enzymes (e.g., subtilisin) have in some cases combined the enzyme soak with the soaking period of the disinfection process. Newer pre-formulated solutions are also added during the disinfection process, but on a daily rather than weekly basis.

Sufficient data should be submitted in the 510(k) to support the effectiveness of the periodic cleaner when used for the minimum time period recommended in the labeling. Consideration should be given to the active ingredients utilized as well as the predicate device labeling for general guidance in determining the recommended period of use.

TESTING MATRIX FOR PERIODIC CLEANERS

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	X	X	X	X
Enzymatic Activity	X FOOTNOTE A	X FOOTNOTE A	X FOOTNOTE A	X FOOTNOTE A
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge	X	X	X	X
Microbial Limits Test (Dry Products/Tablets)	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study		FOOTNOTE B	30 subj/1 mo	60 subj/3 mo

FOOTNOTE A: An In-vitro cleaning effectiveness test should be conducted statistically, using 30-day human-worn daily wear lenses (e.g., group 1 and group IV) to assess the effect of reducing enzymatic activity in this device compared to the predicate device with the same active ingredients.

FOOTNOTE B: Clinical performance data may need to be submitted depending on the physical/chemical, microbiological and toxicological data collected (i.e., a higher concentration of the active cleaning ingredient in a multi-purpose solution with a periodic cleaning claim may require submission of clinical data while an increase in concentration of the active ingredient in a periodic cleaner may not). If necessary, a 30 subject/1 month clinical study should be conducted.

Chemistry:

In addition to the information listed in Section II (General Manufacturing Information) and as outlined in the testing matrix in this section, the following should be provided. (Consideration should be given to tablet preparations compared to liquid preparations.)

1. enzyme disintegration time (for tablet) and enzymatic activity time profile in the proposed diluents as indicated in the labeling;
2. the pH and tonicity of the spent solution when the enzymatic tablet is dissolved in, or added to, the proposed diluents;
3. if the enzymatic tablet is intended to be dissolved in, or added to, a chemical disinfection solution for simultaneously cleaning and disinfecting contact lenses, the effect of the enzyme on the effectiveness of disinfection should be assessed;
4. in-vitro cleaning effectiveness should be conducted for 30 days using human-worn daily wear lenses (group I and group IV for hydrophilic lenses) to assess statistically the effect of reducing enzyme activity in the device compared to the predicate device containing the same enzyme; and
5. if the enzyme in the device in the submission is identical to the enzyme in the predicate device, a side-by-side comparison of the information requested in items 1-3 should be submitted along with a discussion of why the safety of the new device and cleaning effectiveness are equivalent to the predicate device.

Microbiology:

See Testing Matrix for Periodic Cleaners, Section II (General Manufacturing Information) and Section VI (Recommended Test Methods) Micro--Appendix A, for guidance on recommended tests for including in a 510(k).

If a periodic cleaner is indicated for use simultaneously with a chemical disinfecting product, disinfection efficacy testing should be performed with the periodic cleaner present and data submitted in the 510(k).

Toxicology:

See Testing Matrix for Periodic Cleaners and Section VI (Recommended Test Methods) Tox--Appendices A-B, for guidance on recommended tests for including in a 510(k).

Clinical:

See Testing Matrix for Periodic Cleaners for guidance on size and scope of a clinical trial. Further clinical guidance on protocol development is available in Section VI (Recommended Test Methods) Clin--Appendices A-E.

C. CHEMICAL DISINFECTING PRODUCTS FOR CONTACT LENSES

Contact lens disinfection is a critical step in the safe and effective reprocessing of lenses recommended for reuse. For purposes of this guidance document, contact lens disinfection is generally defined as a process that uses one or more contact lens care products designed to eliminate and destroy potentially harmful microorganisms on a contact lens. The contact lens disinfecting products that utilize anti-microbial ingredients for chemical disinfection of lenses are described below. (Heat Disinfection Units are discussed in Section III.F of this guidance.)

1. **Chemical Disinfecting Solution:** A chemical disinfecting solution is generally defined as a contact lens care product containing one or more active ingredients (e.g., preservatives or anti-microbial agents) in sufficient concentrations to destroy harmful microorganisms on the surface of a contact lens within the recommended minimum soaking time.

In order for a contact lens care solution to be labeled as a contact lens "disinfecting solution," it should meet the primary performance criteria of the stand-alone procedure for contact lens disinfecting products [see Section VI (Recommended Test Methods) Micro--Appendix B Part 1 for methodology]. This criteria may also be satisfied by a hydrogen peroxide (H_2O_2) disinfecting solution.

- 2a. **Chemical Disinfection System:** A chemical disinfection system is generally defined as a combination of two or more products, when used in accordance with the labeled directions, results in the cleaning and disinfection of a contact lens.

In order for the contact lens regimen to be labeled as a chemical disinfection system, it should at minimum meet the performance criteria of the regimen procedure [see Section VI (Recommended Test Methods) Micro--Appendix B Part 2].

A chemical disinfection system (also referred to as a chemical disinfection regimen) generally consists of a daily cleaning solution, rinsing solution and soaking solution. Because all steps within the regimen (cleaning, rinsing and soaking) should be completed to obtain adequate contact lens disinfection, special labeling controls are required for these systems [see Section V (Labeling)].

- 2b. **Disinfecting Systems Requiring Neutralization:** Some disinfecting systems may require specially designed lens vials or neutralizing solutions. An example of current technology in this area is a H_2O_2 system. A H_2O_2 system is generally defined as a combination of two or more contact lens care products that, when used in accordance with labeled directions for use, will result in the adequate disinfection of a contact lens. H_2O_2 systems generally consist of the following:

- a. **H₂O₂ Solution:** This product is generally defined as a contact lens solution containing the active ingredient, H₂O₂, in sufficient concentrations to destroy harmful microorganisms on the surface of a contact lens during the minimum recommended soaking time. In some cases, H₂O₂ solution may meet the primary performance criteria of the stand-alone procedure for contact lens disinfecting products in Section VI (Recommended Test Methods) Micro--Appendix B Part 1.
 - b. **Neutralizer:** This product is generally defined as a contact lens care product (e.g., disk, tablet, or solution) containing one or more active ingredients in sufficient concentration to neutralize the irritating and toxic effects associated with the residual H₂O₂ remaining on the lenses after soaking in the H₂O₂ solution. Pre-formulated neutralizing solutions may also be labeled for use as a rinsing and storage solution for contact lenses. A neutralizer is generally considered to be a component of the whole H₂O₂ disinfecting system.
 - c. **Lens Vial:** In addition, the H₂O₂ system may also contain a specially-designed contact lens vial that acts as a lens case to store lenses during the H₂O₂ disinfection process. Many of the currently marketed H₂O₂ systems are uniquely designed to use only those components identified in the labeling for safe and effective use of the system.
3. **Conditioning Solution:** A conditioning solution is a solution that may contain multiple active ingredients (e.g., preservative and ophthalmic demulcents) in sufficient concentration to enhance the wettability of hydrophobic lenses (i.e., RGP and PMMA) prior to insertion and to destroy harmful microorganisms on the surface of the lens during the recommended soaking time.

A conditioning solution should meet, at a minimum, the performance criteria of the regimen procedure. A conditioning solution may be recommended for use with a specific daily cleaner as part of a lens care regimen for soaking and storage of RGP lenses prior to wear. Because of the multiple claims for this type of solution, information should be submitted in a 510(k) to support all claims identified in the labeling for a conditioning solution. These products may also be used to lubricate and rewet RGP lenses prior to insertion in the eye.

Manufacturers who wish to provide eye care practitioners with separate instructions for in-office chemical disinfection and storage of trial lenses should submit a new 510(k) for the additional labeling. These instructions should be intended for reprocessing of trial lenses included as part of a manufacturer's trial lens fitting set or for individual lenses maintained in the practitioner's inventory for reuse between patients. Because there are increased risks associated with the reuse of trial lenses between patients, disinfection and storage claims should be supported by anti-microbial efficacy data, including virucidal efficacy (e.g., H. simplex, Adenovirus).

Manufacturers should include the following in their instructions to eye care practitioners:

- To record the initial storage date and the end of the storage period
- Reminder that disinfecting solutions remain within their expiration date during the entire trial lens storage period
- A visual check for turbidity in storage solution that would indicate contamination
- Instructions for proper care of storage vial to prevent biofilm

At this time, no harmonized industry standards address the issues associated with in-office disinfection and storage of trial lenses. Professional associations such as the American Optometric Association and the American Academy of Ophthalmology publish guidance for practitioners on hygienic management of trial lenses and in-office disinfection. FDA is currently working with the International Standards Organization (ISO) to develop a standardized method to address efficacy criteria and labeling recommendations regarding the disinfection and storage of trial lenses. Additional guidance will be provided as it becomes available.

TESTING MATRIX FOR SOAKING SOLUTIONS FOR DISINFECTION

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	X	X	X	X
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge	X	X	X	X
Disinfection Efficacy	X	X	X	X
Microbial Limits Test (Dry Products/Tablets)	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study		30 subj/1 mo		60 subj/3 mo

TESTING MATRIX FOR NEUTRALIZING PRODUCTS

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	FOOTNOTE A	FOOTNOTE A	FOOTNOTE A	X
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge	X	X	X	X
Microbial Limits Test (Dry Products/Tablets)	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study		30 subj/1 mo	FOOTNOTE B	60 subj/3 mo

FOOTNOTE A: If the spent solution has a pH of 7.2 ± 0.2 and tonicity of 290-320 mOsm/kg, manufacturers are not required, in most instances, to submit compatibility data.

FOOTNOTE B: Clinical performance data may need to be submitted depending on the physical/chemical, microbiological and toxicological data collected. If necessary, a 30 subject/1 month clinical study should be conducted.

TESTING MATRIX FOR CONDITIONING SOLUTIONS

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	FOOTNOTE A	FOOTNOTE A	FOOTNOTE A	X
Wetting Angle	X	X	X	X
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge	X	X	X	X
Disinfection Efficacy	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study		30 subj/1 mo		60 subj/3 mo

FOOTNOTE A: If the conditioning solution has a pH of 6.6-7.8 and tonicity of 290-320 mOsm/kg, manufacturers are not required, in most instances, to submit compatibility data.

Chemistry:

In addition to the information listed in Section II (General Manufacturing Information) and as outlined in the testing matrices in this section, the following should be provided, when appropriate:

For conditioning solutions:

1. wetting angle of hydrophobic lenses in conditioning solution as a function of soaking time; and
2. the pH, tonicity and viscosity of the conditioning solution.

For chemical disinfection solutions:

pH and tonicity of the chemical disinfection solution used for hydrophilic contact lenses.

For H₂O₂ systems:

1. the pH and tonicity for the H₂O₂ and neutralization solutions;
2. the pH, tonicity and residual H₂O₂ of the spent solution following neutralization for a H₂O₂ disinfecting system;
3. for neutralization solution, tablets, or disks, a neutralization profile under the recommended care regimen should be provided:
 - a. if a disk is used, manufacturers should establish a discard date based upon the maximum number of effective uses of the neutralization disk; and
 - b. if a time-delayed tablet is used for a disinfecting/neutralization system, the following additional information is needed:
 - (1) materials for coating the tablet (e.g., nature of polymer, average molecular weight, molecular weight distribution, and swelling); and
 - (2) QA/QC procedures and sampling plan for time-delayed release tablet.

Microbiology:

See Section II (General Manufacturing Information), the applicable testing matrices for Soaking Solutions for Disinfection, Neutralizing Solutions, and Conditioning Solutions, and Section VI (Recommended Test Methods) Micro--Appendices A-B for guidance on recommended microbiology tests for including in the 510(k).

The disinfection efficacy of a disinfecting solution, system, or a conditioning solution should be evaluated by the stand-alone procedure [see Section VI (Recommended Test Methods) Micro--Appendix B, Part 1]. If the

product does not meet the primary criteria, but does meet the secondary criteria, the product should then be evaluated by the regimen procedure (Micro--Appendix B, Part 2).

Toxicology:

See Testing Matrices for Soaking Solutions for Disinfection, Neutralizing Solutions, and Conditioning Solutions and Section VI (Recommended Test Methods) Tox--Appendices A-B.

For H₂O₂ disinfection systems, toxicology testing should be performed on the neutralized disinfection solution (i.e., spent solution).

Clinical:

See applicable Testing Matrices for Soaking Solutions for Disinfection, Neutralizing Solutions, and Conditioning Solutions for guidance on recommended size and scope of clinical trials. Further guidance on protocol development is available in Section VI (Recommended Test Methods) Clin--Appendices A-E.

D. MULTI-PURPOSE SOLUTION

A multi-purpose solution is generally defined as a single contact lens care solution that contains multiple active ingredients in sufficient concentrations to perform the functions of daily cleaning, chemical disinfection, rinsing and storage of contact lenses. Because of the multiple uses claimed for this individual solution, information should be submitted in a 510(k) to support all claims identified in the labeling. In addition, strict attention should be paid to the labeling for this product to assure that adequate directions for use (e.g., rubbing and rinsing times for daily cleaning, soak times for disinfection, and maximum storage times following disinfection) are provided for all intended uses identified above.

A contact lens solution that cannot perform all of the functions identified above should not be labeled as a multi-purpose contact lens care solution [see Labeling section for multi-purpose solutions below and Section V (Labeling) for further guidance on labeling for multi-purpose contact lens solutions].

Chemistry:

See applicable testing matrices and Section VI (Recommended Test Methods) for the recommended manufacturing/chemistry tests for the applicable indications (e.g., daily cleaning and disinfection solutions).

Microbiology:

See Section II (General Manufacturing Information), applicable testing matrices, and Section VI (Recommended Test Methods) for the recommended microbiology tests for the applicable indications (e.g., daily cleaning and disinfection solutions).

Toxicology:

See applicable testing matrices and Section VI (Recommended Test Methods) for the recommended toxicology tests for the applicable indications (e.g., daily cleaning and disinfection solutions).

Clinical:

See applicable testing matrices for guidance on size and scope of a clinical trial for the applicable indications (e.g., daily cleaning and disinfection solutions). Further clinical guidance on protocol development is available in the Section VI (Recommended Test Methods) Clin--Appendices A-E.

Labeling:**Policy for Multi-Purpose Solutions:**

Applicants are advised that a multi-purpose solution should not be labeled as an ALL-IN-ONE solution. CDRH believes that an ALL-IN-ONE claim can be misleading for these products because lubricating

and rewetting drops as well as enzyme treatment are utilized for complete lens care.

Multi-purpose products are usually labeled for cleaning and disinfecting. It is potentially unsafe to label a product intended for cleaning and disinfecting for in-eye use as well since consumers may inappropriately use other cleaners and disinfecting solutions that are not compatible with in-eye use. A multi-purpose solution should not be labeled for lubricating and rewetting lenses during wear even if the chemical compositions of the multi-purpose solution and lubricating and rewetting drops are identical.

CDRH maintains a working policy that lubricating and rewetting drops should be packaged in bottle sizes not to exceed 30 ml in order to minimize the risks of contamination and possible eye infections and facilitate ease of use.

Therefore, based on concerns for contamination during use and consumer misuse and confusion, it is CDRH's policy to discourage manufacturers from labeling multi-purpose solutions for in-eye indications for use. CDRH believes that a policy of limiting indications for in-eye use solutions to that single intended use enhances product safety and encourages consumer compliance with safe lens care practices.

See Section V (Labeling) for general guidance for developing labeling for contact lens care products. In addition, predicate device labeling should also be used as general guidance for labeling new multi-purpose solutions.

E. IN-EYE CONTACT LENS SOLUTIONS (Lubricating and/or Rewetting Drops)

An in-eye solution for use with contact lenses (e.g., lubricating and/or rewetting drops) is generally defined as a contact lens care solution containing one or more active ingredients (e.g., ophthalmic demulcents) in sufficient concentration to alleviate symptoms of discomfort from contact lens wear by a physical means as opposed to a pharmacological action generally associated with OTC in-eye solutions regulated as drugs. A preparation labeled for use with contact lenses which contains an ophthalmic demulcent, as listed in 21 CFR 349.12, will qualify as a lubricating drop based on formulation. All predicate lubricants to date contain a demulcent. If a preparation does not contain a demulcent (e.g., a small volume unit-dose saline), it would qualify as a rewetting drop, not as a lubricating drop. Predicate device labeling should be used as a comparison for intended use.

The devices in this category of products, generally referred to as lubricating and/or rewetting lens drops, are intended for direct instillation in the eye while wearing contact lenses to achieve the intended purpose. These products may also be used to lubricate and/or rewet lenses prior to insertion in the eye.

Policy for Multi-Dose In-Eye Contact Lens Solutions:

CDRH believes that lubricating and rewetting drops should be packaged in bottle sizes not to exceed 30 ml in order to minimize the risks of contamination and possible eye infections and facilitate ease of use. The risk of contamination with multi-dose in-eye contact lens solutions should be further minimized by formulating the product to contain one or more suitable harmless substances such as a preservative, that will inhibit the growth of microorganisms. Alternatively, in-eye contact lens solutions may be packaged as to volume and type of container and appropriately labeled to afford adequate protection and minimize the hazard of injury resulting from contamination during use (e.g., unpreserved in unit-dose containers).

CDRH recognizes that a solution manufacturer that produces a product with an identical formulation to that of an in-eye lens solution, such as a saline or conditioning solution, which is marketed in a size larger than 30 ml will be discouraged by this policy from labeling the solution for in-eye use. Also, the Policy for Multi-Purpose Contact Lens Solutions (see Section III D, Multi-Purpose Solution) would discourage labeling certain products for in-eye use indications.

In addition, it is encouraged that labeling for multi-dose in-eye contact lens solutions include instructions to discard the solution after a specified period after opening. If a discard date is proposed, it should be based on the package size, projected number of uses, and frequency of use.

CDRH believes that a policy of limiting indications for in-eye use solutions to that single intended use enhances product safety and encourages consumer compliance with safe lens care practices.

TESTING MATRIX FOR IN-EYE CONTACT LENS PRODUCTS

	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients In Lower Concentrations Than Marketed Products	New Ingredients for Ophthalmic Use or Different Active Ingredient
CHEMISTRY				
Stability	X	X	X	X
Solution Compatibility	FOOTNOTE A	FOOTNOTE A	FOOTNOTE A	X
MICROBIOLOGY				
Sterility	X	X	X	X
Preservative Effectiveness with Rechallenge	X	X	X	X
Stability	X	X	X	X
TOXICOLOGY				
In-Vitro Cytotoxicity	X	X	X	X
Acute Ocular Irritation	X	X	X	X
Acute Oral Toxicity				X
Sensitization				X
In-Vivo Ocular Biocompatibility				X
CLINICAL				
Recommended Size/Scope of Clinical Study	30 subj/1 mo	30 subj/1 mo	30 subj/1 mo	60 subj/3 mo

FOOTNOTE A: If the in-eye contact lens solution has a pH of 6.6-7.8 and tonicity of 290-320 mOsm/kg, manufacturers are not required, in most instances, to submit compatibility data.

Chemistry:

See Section II (General Manufacturing Information) Testing Matrix for In-Eye Contact Lens Solutions, and Section VI (Recommended Test Methods) Chem--Appendices A and C, for guidance on recommended tests for including in a 510(k).

In addition, for lubricating solutions, manufacturers should identify and characterize the ophthalmic demulcent as listed in 21 CFR 349.12 and provide pH, tonicity, and viscosity.

Microbiology:

See Section II (General Manufacturing Information), Testing Matrix for In-Eye Solutions, and Section VI (Recommended Test Methods) Micro--Appendices A-B, for guidance on recommended tests for including in a 510(k).

Toxicology:

See Testing Matrix for In-Eye Solutions and Section VI (Recommended Test Methods) Tox--Appendices A-B, for guidance on recommended tests for including in a 510(k).

Clinical:

See Testing Matrix for In-Eye Solutions for guidance on size and scope of a clinical trial. Further clinical guidance on protocol development is available in Section VI (Recommended Test Methods) Clin--Appendices A-E.

Applicants are reminded that FDA generally considers clinical studies of certain solutions intended to be used directly in the eye to be significant risk investigations which require both IRB and FDA review and approval prior to initiating clinical studies. Applicants should refer to the "Introduction" section for guidance concerning significant risk clinical studies.

F. HEAT DISINFECTION UNITS

A heat disinfection unit is a contact lens care product intended to disinfect soft (hydrophilic) contact lenses by means of heat. Heat disinfection units act by transferring sufficient heat to a contact lens case containing the lenses and saline solution for a specified period of time to destroy harmful microorganisms on the lenses.

Manufacturing/Chemistry:

The following manufacturing/chemistry guidance should be used when submitting a 510(k) for a heat disinfection unit:

A positive function/failure indicator should be installed in the heat unit circuitry. Any 510(k) for a heat unit without a positive function/failure indicator should have an acceptable justification for not having the indicator. A positive function/failure indicator is one that:

- indicates that the unit is heating or on only when heat is being generated or electrical current is flowing through the heat element; and
- indicates that the unit is cool or off only when the temperature has dropped towards room temperature or when no current is flowing in the heat unit.

Units that meet this definition would include:

- electrically timed or thermostatically controlled units in which a light emitting indicator is effectively in series with the heater; and
- units that use a temperature sensing element that changes color or provides a similar distinct indication between room temperature and elevated temperature.

A 510(k) for a heat disinfection unit should contain:

1. time-temperature curves from a statistically significant sample of units which demonstrate that the lower three standard deviation points of the distribution of time-temperature curves is greater than the minimum time-temperature necessary for effective heat disinfection;
2. electric circuitry and safety features;
3. certification that the heat disinfection unit conforms to the requirements of applicable electrical safety standards [e.g., Underwriters Laboratories (UL) 1431 entitled "Personal Hygiene and Health Care Appliances"].
4. QA/QC procedures and sampling techniques (e.g., Military Standard 105E) for critical components;

5. QA/QC procedures and sampling techniques (e.g., Military Standard 105E) for final device; and
6. 30-cycle lens compatibility under the recommended care regimen.

Microbiology:

Microbiology data are generally not required for heat disinfection units provided the heat disinfection cycle time and temperature are equivalent to those of the predicate device (e.g., 80°C for 10 minutes).

If an alternative heat disinfection cycle is proposed, microbicidal efficacy should be demonstrated by a microbial challenge test utilizing at least 10 units and 20 lenses each from lens groups I and IV. The following procedure is recommended:

Inoculate lenses with approximately 1×10^6 organisms Enterococcus faecalis (formerly Streptococcus faecalis) (recommended strain: Ward's Natural Science Establishment #85 W 1100) in organic soil, and expose to the proposed heat disinfection cycle. Prepare the organic soil inoculum as described in Section VI (Recommended Test Methods) Micro--Appendix B, Part 2:III.B and an inoculum control as described in Micro--Appendix B, Part 2:D.1. After heat disinfection, culture lenses as described in Micro-Appendix B, Part 2:III.C.3. If a preserved saline is used in the heat disinfection process, use a recovery medium that contains one or more neutralizing agents. Validate the recovery medium as described in Micro--Appendix B, Part 2:D.2.

All lens and test filter combinations should show no growth.

Toxicology:

Toxicology data are generally not required for heat disinfection units provided the heat disinfection unit is essentially identical to the predicate device unless the heat unit is also designed for use as a lens case. In the latter situation, toxicology information similar to that for lens cases should be provided.

Clinical:

Clinical data are not generally required for heat disinfection units provided the specifications for the heat disinfection unit are substantially equivalent to the predicate device.

G. CONTACT LENS CASES

A contact lens case is a lens care product to be used by the contact lens wearer or practitioner for storing contact lenses while not being worn. Contact lens cases are especially designed for use in chemical, heat or H₂O₂ disinfecting systems. Not included in this definition are lens cases intended by the manufacturer only for shipping the lenses in a dry state.

Manufacturing/Chemistry:

The following manufacturing/chemistry information should be provided in the 510(k):

1. Engineering drawing and a brief description of polymeric materials used.
2. Physical and chemical data of polymeric materials used and name and address of the manufacturer.
3. If the lens case is used in heat disinfection, the applicant should provide proof that the lens case can withstand repeated heat disinfection. Physical and chemical data of polymeric material (e.g., heat distortion temperature or glass transition temperature may be used to substantiate this indication). In general, a lens case used in heat disinfection should contain a rubber gasket.
4. The volume capacity of the lens case (e.g., should be of sufficient volume to assure that the lens remains completely immersed under conditions of use).
5. Certification that colorants used in the manufacture of the lens case are insoluble in water [this information is often found in the material safety data sheet (MSDS)].

Microbiology:

Microbiology testing requirements for lens cases are dependent upon claims made in the labeling. In general, microbiology issues pertaining to contact lens cases are covered by the warning recommended in the labeling [see Section V (Labeling)].

Toxicology:

Toxicology data from the following tests conducted on both the plastic and gasket materials should be provided:

1. Systemic Toxicity Test (see USP/NF XXII for methodology)
2. Acute Ocular Irritation Test
3. In-Vitro Cytotoxicity Test

See Section VI (Recommended Test Methods) Tox--Appendices A-B for guidance.

CDRH is aware that suppliers of plastic and other materials generally provide MSDSs to manufacturers of devices using their materials. Manufacturers are encouraged to carefully scrutinize the information provided in these MSDSs to determine if they contain the needed toxicology information before initiating the recommended tests. If the information is included on the MSDS, the MSDS may be provided in lieu of toxicology data. MSDSs should be provided in 510(k)s.

Clinical:

Clinical data are generally not required to be submitted in a 510(k) for lens cases. However, manufacturers should consider the impact of design, materials and intended use on need for clinical performance data.

H. CONTACT LENS ACCESSORIES (e.g., Mechanical Cleaning Aids and Accessory Cleaning Pads)

Contact lens accessories (e.g., mechanical cleaning aids and accessory cleaning pads) are devices used as cleaning aids in conjunction with contact lens cleaning solutions.

1. Mechanical Cleaning Aid: A mechanical cleaning aid may be available as a hand or battery-operated or electrical device that aids in cleaning contact lenses by generating ultrasound, tumbling motions, or vibrations for the cleaning solution while it cleans. It may also act as a receptacle during the rinsing or chemical disinfecting steps in the lens care regimen.

Although the mechanical cleaning aid has not been officially classified, in the past CDRH has evaluated requests for marketing such devices through the 510(k) process. With the availability of this special controls document, it is our present intention to allow manufacturers of SE mechanical cleaning aids to label their devices for use as accessories to approved contact lens cleaning solutions.

Applicants are advised that if the new device contains a new technology, performance data (e.g., cleaning effectiveness) may be required to demonstrate substantial equivalence. DOD should be contacted concerning protocol development for performance data for 510(k)s for devices containing new technology (telephone number at the end of Introduction section).

Manufacturing/Chemistry:

The following information should be provided in the 510(k) for the mechanical cleaning aids (as applicable):

- a. a detailed description of the device and engineering drawings;
- b. a mode of action (e.g., ultrasound);
- c. electric circuitry and safety features if applicable [e.g., for all electrical devices, certification that they conform to the requirements of applicable electrical safety standards (e.g., UL 1431 entitled, "Personal Hygiene and Health Care Appliances")]; and
- d. if the device generates heat when used according to the directions in the labeling, an assessment of this affect on the lens parameters and durability.

Microbiology:

Microbiology testing requirements for mechanical cleaning aids are dependent upon claims made in the labeling. In general, sufficient microbiology data should be submitted to support all claims being made in the labeling.

Toxicology:

Toxicology data from the following tests conducted on the materials (e.g., gaskets, plastics, etc.) that come in contact with the solutions should be provided:

- a. Systemic Toxicity Test (see USP/NF XXII for methodology)
- b. Acute Ocular Irritation Test
- c. In-Vitro Cytotoxicity Test

See Section VI (Recommended Test Methods) Tox--Appendices A-B for guidance.

CDRH is aware that suppliers of plastic and other materials generally provide MSDSs to manufacturers of devices using their materials. Manufacturers are encouraged to carefully scrutinize the information provided in these MSDSs to determine if they contain the needed toxicology information before initiating the recommended tests. If the information is included on the MSDS, the MSDS may be provided in lieu of toxicology data. MSDSs should be provided in 510(k)s.

Clinical:

Clinical data are generally not required to be submitted in a 510(k) for mechanical cleaning aids. However, manufacturers should consider the impact of design, materials and intended use on need for clinical performance data in order to provide adequate directions for use of the device.

2. Accessory Cleaning Pads: Accessory cleaning pads are made of materials that generally contain mildly abrasive surfaces. The pads are intended to be used in conjunction with contact lens cleaning solutions to aid in lens cleaning by minimizing direct contact with the hands.

Manufacturing/Chemistry:

The following manufacturing/chemistry information should be provided in the 510(k):

- a. compatibility data that demonstrate the cleaning pad will not damage (e.g., scratch) the lenses; and
- b. a detailed description of the chemical components of the device.

Microbiology:

The applicant should identify and provide information to address all potential microbial concerns raised by reuse of the pad, if the pads are to be reused, in which case cleaning instructions for the pad should be provided. In addition, appropriate lens cleaning instructions, warnings, and precautions should be included in the labeling.

Toxicology:

The following toxicology information should be provided in the 510(k):

Data demonstrating that any materials coming in contact with the cleaning solutions are not eye irritants. This information may be provided in an MSDS or from testing conducted in accordance with the Acute Ocular Irritation Test found in Section VI (Recommended Test Methods) Tox-- Appendix-A.

Clinical:

Clinical data are not generally required to be submitted in a 510(k) for accessory cleaning pads. However, manufacturers should consider the impact of design, materials and intended use on need for clinical performance data.

IV. MODIFICATIONS OF APPROVED CONTACT LENS CARE PRODUCTS REQUIRING A 510(k):

- A. A manufacturer with a PMA or a 510(k) for a contact lens care product may, for a variety of reasons, want to modify the device. Based on our knowledge and experience with contact lens care products, CDRH has listed the following changes to approved care products that could significantly affect safety and effectiveness of the device and thus require 510(k) clearance under 21 CFR 807.81(a). These changes include, but are not necessarily limited to, the following:

1. a change in an active ingredient or concentration of the active ingredient;

NOTE: Although this guidance document focuses primarily on active ingredients, manufacturers should also assess the effects of inactive ingredients (e.g., buffering agents and tablet coatings) on such factors as pH, tonicity, preservative effectiveness, solution compatibility with lenses, and preservative uptake/release to determine if the change significantly affects safety and effectiveness of the device and, therefore, requires submission of a 510(k).

2. addition of a new ingredient for ophthalmic use;
3. a change in preservative or preservative concentration in solutions;
4. a major change or modification in the product specific intended use of the device or indication for use (e.g., addition of performance information in the labeling that implies that the device can be used for previously unmentioned product specific use such as adding a cleaning claim to a disinfecting solution to create a multi-purpose solution or claiming that the device can be used for a different type of lens such as hydrophobic when previously hydrophilic was indicated);
5. changes in the directions for use affecting product performance (e.g., decreased soak times for disinfecting solutions or periodic cleaners);
6. a change in the type of container/closure and delivery systems of a contact lens solution [e.g., changing from a plastic bottle to an aerosol can or changing from a chemical preservative system to a physical barrier (e.g., filters) preservative system for contact lens solution];
7. changes in dosage form (e.g., adding tablet coatings for time release or changing from a liquid to tablet preparation of the active agents); and

8. addition or deletion of a contraindication:

NOTE: Manufacturers should submit a Special 510(k)--Changes Being Effected to add a contraindication. Applicants should refer to existing FDA policy for guidance on deciding when to submit a 510(k) for a labeling change to an existing device. Deletion of a contraindication would be expected to change the intended use and would, therefore, require submission of a new 510(k).

- B. Listed below are some examples of changes that should not require a 510(k) to be submitted provided the change adheres to current FDA policies and is adequately documented:

1. addition of private label distributors who are not manufacturing the product;
2. extension of the expiration date according to a cleared/approved protocol;
3. a change to a smaller or larger size container made from identical materials provided stability studies are done according to a cleared/approved protocol and product specifications remain unchanged. If the new container is no more than 8 times larger than the smallest size container for which stability/sterility testing data have previously been evaluated, no additional stability studies are necessary. In accordance with 21 CFR 800.10(b), contact lens solutions should be so packaged as to volume and type of container to minimize contamination during use. The largest size product container currently marketed is a 16 fl. oz size. [See Section VI (Recommended Test Methods, Shelf-Life Protocol) in the Appendices];
4. changes in packaging material (e.g., high density polyethylene to low density polyethylene) provided: (1) the new materials meet USP requirements (Containers for Ophthalmics Plastics--Biological Test Procedures) and leachables do not cause eye irritation, (2) the new materials do not compromise sterility package integrity, and (3) shelf-life is re-established according to a cleared/approved protocol.
5. changes in container shapes;
6. changes in trade name provided the new trade name does not misbrand the device;
7. adding a new manufacturing site without changing the manufacturing processes;
8. reformatting or editorial changes in labeling;

9. changes from one traditional sterilization method utilized for the sterilization of the final product, raw materials or packaging materials to another traditional method (e.g., from ETO to gamma radiation) provided: (1) the new method meets an acceptable SAL (10^{-6} for terminal sterilization and 10^{-3} for aseptic processing) and does not change the product performance specifications and (2) shelf-life is re-established according to a cleared/approved protocol;
10. documented changes in manufacturing process that could not significantly affect the safety or effectiveness of the device and are implemented in accordance with GMP requirements; and
11. adding or strengthening precautions or warnings in accordance with existing FDA policy.

NOTE: Manufacturers should monitor device usage and periodically revise their warnings and precautions sections based on use experience. A 510(k) for such a change in precautions or warnings generally does not require submission of a 510(k) unless the change results in a new intended use. However, manufacturers should document these changes in their files.

If after reviewing the above changes specifically identified in this product specific guidance document as needing a new 510(k), applicants are unable to determine whether a 510(k) is required for a proposed modification to a contact lens care product, they may consult existing FDA policy (e.g., Blue Book Memorandums) on modifications needing a 510(k).

V. LABELING

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V. LABELING**A. Introduction:**

This section of the guidance provides general information on the applicable regulations and requirements for labeling of contact lens care products, what information should be submitted for review of a 510(k) for these devices, and guidance on preparing labeling for contact lens care products [e.g., contact lens solutions and tablets, lens cases, heat disinfection units, salt tablets/capsules, and contact lens accessories (e.g., mechanical cleaning aids and accessory cleaning pads)] respectively.

Contact lens care products are subject to the general labeling requirements for all medical devices outlined in 21 CFR 801. Contact lens solutions are further subject to 21 CFR 800.10, Contact Lens Solutions; Sterility and 21 CFR 800.12, Contact Lens Solutions and Tablets; Tamper-resistant Packaging.

CDRH considers adequate labeling to be an important safeguard (special control) for assuring that new contact lens care products are substantially equivalent in terms of safety and effectiveness to legally marketed devices. Applicants are encouraged to provide predicate device labeling in their 510(k) submissions.

B. Labeling Information Required in an Original 510(k) or 510(k) for a Modification:

Under 21 CFR 807.87(e), a 510(k) applicant is required to submit proposed labels, labeling, and advertisements sufficient to describe the device (composition), its intended use (i.e., indications for use), and the directions for its use. This basic information is required before CDRH can render a substantial equivalence determination for either an original 510(k) or for a 510(k) that includes modifications (e.g., changes in device description, intended use, or directions for use) if the modification significantly affects safety or effectiveness of the device. In addition, manufacturers should submit a 510(k) before making a change such as adding or deleting a contraindication (see Section IV).

C. Regulatory Guidance:

Information that generally accompanies the sale and distribution of contact lens care products can include, but is not limited to, such printed matter as outer carton labeling, bottle or device label, and (for solutions) a package insert. CDRH considers such printed matter to be labeling as described in Section 201(m) of the act, which also provides general guidance as to the type of information that should be included in contact lens care product labeling. Because labeling is not approved when 510(k) clearance is granted, the manufacturer should be advised that once the device is marketed, the device is required to be labeled in accordance with applicable regulations which include, among other things, prohibition against misbranding and including false and misleading information in the labeling. In order to avoid violating the labeling regulations, applicants should scrutinize their labeling in

draft for words or phrases that are exaggerated, potentially ambiguous, or subjective as well as unsubstantiated statements, claims, or puffery. Such words or phrases in labeling may be considered false or misleading, and if marketed with false or misleading claims, could cause the manufacturer to be subject to regulatory action. CDRH urges applicants to carefully adhere to pertinent labeling regulations and DO NOT PRINT LABELING IN FINAL FORM until a substantial equivalency letter is received.

Pertinent Labeling Regulations:

- Definitions of "label" and "labeling" [Sections 201(k) and 201(m) of the act].
- Information required in a premarket notification submission pertaining to labeling (21 CFR 807.87(e)).
- General Labeling Provisions (21 CFR 801); Contact Lens Solutions; Sterility (21 CFR 800.10); and Contact Lens Solutions and Tablets; Tamper-resistant Packaging (21 CFR 800.12).
- Explanation of what causes a device to be misbranded and false and misleading labeling (Section 502 of the Act, 21 CFR 801.6, 807.39, and 807.97).

The following references or their most recent revisions may be consulted for further guidance:

1. Labeling Regulatory Requirements for Medical Devices. This publication discusses such areas as advertising material considered labeling, what is false and misleading labeling, adequate directions for use, and provides examples of ways that device manufacturers can comply with labeling requirements. Copies of this publication can be obtained by contacting DSMA (fax and telephone numbers are at the end of the Introduction section).
2. Device Labeling Guidance #G91-1 (Office of Device Evaluation Blue Book Memorandum). This guidance provides detailed interpretations of applicable labeling regulations, and can be obtained from DSMA (fax and telephone numbers are at the end of the Introduction section).
3. Human Factors Principles of Medical Device Labeling. This guidance pertains to labeling for all medical devices. It contains basic principles for the effective design of instruction booklets for medical device use. Along with the principles are selected examples (graphics, cleaning steps, etc.) abstracted from a generic model booklet. These examples do not contain all elements required by 21 CFR 801, but they embody human factors principles and may be used, along with predicate labeling, as a guide in writing your labeling. This guidance is available by contacting DSMA (fax and telephone numbers are at the end of the Introduction section).

D. Labeling Examples:

An outline and specific device information that should be included in pre-formulated solution and tablet labeling based upon predicate device labeling is provided in Labeling--Appendix A.

Labeling--Appendix A also includes an example of a package insert for aerosol saline solution that incorporates principles taken from labeling entitled, "Improved Patient Instructions for Care of Soft Contact Lenses," that was prepared by a CDRH focus group based upon a study using consumers and Write-It-Right principles (Write-It-Right booklet is available by contacting DSMA (fax and telephone numbers are at the end of the Introduction section)).

Applicants are advised that although it is not required that they use the exact wording in the product specific contraindications, warnings, precautions, etc., provided in this outline, FDA recommends the basic content not be changed. Thus, to avoid the potential for changes in meaning, we encourage applicants to exercise care.

An applicant may follow the format using Write-It-Right principles or follow the format in the most recently marketed predicate device labeling.

In cases where individual devices require unique warnings, precautions, contraindications, etc., in addition to those recommended in the specific device information sections, applicants should provide sufficient information in the 510(k) to support the inclusion of these unique statements in their labeling.

Labeling--Appendices B-F contain examples of labeling for lens cases, heat disinfecting units, salt tablets/capsules systems, and contact lens accessories (e.g., mechanical cleaning aids and accessory cleaning pads), respectively.

If further labeling guidance is required, applicants may contact DOD (fax and telephone numbers are at the end of the Introduction section).

LABELING--APPENDIX A

Package Insert for Pre-Formulated Solutions and Tablets

Labeling--Appendix A includes (1) an outline and specific device information that should be included in a package insert for pre-formulated solutions and tablets, (2) an outline of specific device information that should be included on the outer carton and bottle labeling for these devices, and (3) an example of a package insert for aerosol saline using Write-It-Right principles.

In preparing labeling, applicants should fill in the brackets by including specific information pertaining to the device in the 510(k). Predicate device labeling, the outline below, and the example provided in this section may be used as further guidance.

SAMPLE PACKAGE INSERT

PLEASE READ CAREFULLY AND KEEP THIS PACKAGE INSERT FOR FUTURE USE.

DESCRIPTION:

[Include "sterile" if it is a solution; list active ingredients and quantitate the preservative(s) 00.0%] [optional, list inactive ingredients]. When applicable, include the following additional descriptive information:

isotonic
buffered
preserved/unpreserved
propellants
enzyme
tablet, disk, or [describe]]

ACTIONS:

[Include a concise description of the function of the device (i.e., how the device works in relation to the contact lens). When applicable, the actions may be listed with the indications (i.e., INDICATIONS/ACTIONS)].

INDICATIONS (USES):

[Include a description of the proper use of the device. NOTE: The indications should be essentially the same as the predicate device.]

CONTRAINDICATIONS:

Contraindications describe situations in which the device should not be used because the risk of use clearly outweighs any possible benefit. If there are no contraindications, include the statement: "There are no known contraindications for use of this product." Include all contraindications specific to your device. Listed below is a general contraindication.

For all contact lens pre-formulated solutions:

- If you are allergic to any ingredient in this product, DO NOT use.
- Add additional contraindications if applicable to specific device.

WARNINGS:

Warnings include serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. Listed below are (1) general warnings that pertain to all pre-formulated solutions and tablets and (2) product specific warnings. Include those general and specific warnings that apply to the device in the 510(k).

General Warnings:

- To avoid contamination, DO NOT touch tip of container to any surface. Replace cap after using.
- To avoid contaminating your solution, DO NOT transfer to other bottles or containers.
- Add additional warnings if applicable to specific device.

Product Specific Warnings:

Saline Solutions: Add the following specific warnings following heat disinfection (when applicable):

- To minimize the risk of contamination, keep lenses in the unopened case until ready to wear.
1. **Aerosol Salines**
 - Contents under pressure, DO NOT spray directly into the eye as serious injury to the eye may result.
 - DO NOT puncture or incinerate can.
 - DO NOT store at temperature above 120°F.
 - Always spray a small amount of solution into the sink to clear the nozzle of contaminants before spraying the saline onto your lenses.
 2. **Unpreserved Saline**
 - To minimize the risk of eye infection DO NOT use this solution beyond the recommended discard date.

3. Unit Dose Saline

- This product is provided in a single dose package that does not contain preservatives. To minimize the risk of contamination and possible eye infection, DO NOT save and reuse any unused saline. Discard the package immediately after use.

Daily Cleaners:

- DO NOT use directly in the eye. Solution may cause severe irritation, burning and stinging.

Periodic Cleaners:

- DO NOT dissolve enzyme tablets in distilled or tap water. Distilled water and tap water are non-sterile. Use of non-sterile products may lead to microbial contamination of lenses which can cause serious eye infections.
- After cleaning with enzyme cleaner, your lenses should be cleaned with a daily cleaner, rinsed and disinfected. Failure to do so may result in eye irritation, burning, or stinging.
- DO NOT put solution directly in the eye as severe irritation, burning and stinging may result.

Chemical Disinfecting Solutions/Systems and Conditioning Solution:

NOTE: No individual product within a chemical disinfection regimen should be labeled as the "disinfecting solution" unless it can meet the primary criteria of the stand-alone microbiology disinfection test (as referenced in Section VI, Recommended Test Methods, Micro--Appendix B Part 1). Chemical disinfection regimens which meet the regimen procedure criteria may be labeled, for example, as having a starting solution and a finishing solution or as having a cleaning solution and a soaking solution, but no individual product should be labeled as the disinfecting solution.

- DO NOT use with heat (thermal) disinfection unless specifically indicated in labeling.

Warnings for Hydrogen Peroxide Disinfecting Solutions:

- KEEP [TN] disinfecting solution (hydrogen peroxide) OUT OF THE EYES. ALWAYS USE [TN] (neutralizer) with [TN] disinfecting solution to NEUTRALIZE YOUR LENSES BEFORE APPLYING THEM TO YOUR EYES. If [TN] disinfecting solution accidentally comes in contact with the eyes, it may cause burning, stinging or redness. Remove your lens(es) immediately and flush your eyes with a large amount of water or sterile saline. If burning or irritation continues, seek professional assistance.

- Keep [TN] disinfecting solution (hydrogen peroxide) out of the reach of children. If accidentally swallowed, an upset stomach and vomiting may result. Seek immediate professional medical assistance or contact a poison control center.
- Not for use with heat (thermal) disinfection because [state reason].

Warnings for Neutralizing Products (when applicable):

- This tablet is not to be taken internally. If accidentally swallowed, an upset stomach and vomiting may result. Seek immediate professional medical assistance or contact a poison control center.
- DO NOT crush the [TN] Neutralizing Tablet. If a crack occurs in the coating, the tablet may begin to neutralize the [TN] Disinfecting Solution before adequate disinfection occurs.
- DO NOT use [TN] Neutralizer disk for more than XXX uses or XX months of daily use. **[Note:** Uses and time period to be determined by testing data.]

Warnings for Conditioning Solutions:

- DO NOT use with soft (hydrophilic) contact lenses. Soft (hydrophilic) contact lenses can absorb solution components that may cause severe irritation, burning and stinging of the eyes.

In-Eye Contact Lens Solutions:

- To minimize the risk of contamination and eye infection, DO NOT use beyond the discard date on the bottle label (if applicable).

The following non-product specific warnings have been included in predicate device labeling (as applicable) as a "public service" announcement:

Warnings for Hydrophilic Contact Lens Products:

Warnings: PROBLEMS WITH CONTACT LENSES AND LENS CARE PRODUCTS COULD RESULT IN SERIOUS INJURY TO THE EYE. Follow your eye care practitioner's directions and all labeling instructions for proper use and care of your lenses and lens care products, including the lens case. Eye problems, including corneal ulcers, can develop rapidly and lead to loss of vision. Daily wear lenses are not indicated for overnight wear and should not be worn while sleeping. Clinical studies have shown the risk of serious adverse reactions is increased when these lenses are worn overnight. Extended wear lenses should be regularly removed for cleaning and

disinfection or for disposal and replacement on the schedule prescribed by your eye care practitioner. Clinical studies have shown that there is an increased incidence of serious adverse reactions in extended wear contact lens users as compared to daily wear contact lens users. Studies have also shown that the risk of serious adverse reactions increases the longer extended wear lenses are worn before removal for cleaning and disinfection or for disposal and replacement. Studies have also shown that smokers have a higher incidence of adverse reactions. If you experience eye discomfort, excessive tearing, vision changes, or redness of the eye, immediately remove your lenses and promptly contact your eye care practitioner. All contact lens wearers should see their eye care practitioner as directed.

Warnings for Hydrophobic Contact Lens Products:

Warnings: PROBLEMS WITH CONTACT LENSES AND LENS CARE PRODUCTS COULD RESULT IN SERIOUS INJURY TO THE EYE. Follow your eye care practitioner's directions and all labeling instructions for proper use and care of your lenses and lens care products, including the lens case. Eye problems, including corneal ulcers, can develop rapidly and lead to loss of vision. Daily wear lenses are not indicated for overnight wear and should not be worn while sleeping. If you experience eye discomfort, excessive tearing, vision changes, redness of the eye, immediately remove your lenses and promptly contact your eye care practitioner. All contact lens wearers should see their eye care practitioner as directed.

Listed below is a general warning taken from the Write-It-Right example that applies to both soft (hydrophilic) and rigid gas permeable contact lenses:

Warning: Serious injury to the eye and loss of vision may result from problems with contact lenses and lens care solutions. Eye problems, including corneal ulcers and infections, can develop rapidly. Immediately remove your lenses and call or visit your eye care practitioner if you experience any adverse reactions such as: eye discomfort, excessive tearing, vision changes, pain, unusual eye discharge, sensitivity to light, or redness of the eye.

PRECAUTIONS:

Precautions include information regarding any special care to be exercised by the user for the safe and effective use of the device. Listed below are (1) general precautions that pertain to all pre-formulated solutions and tablets and (2) product specific precautions. Include those general and specific precautions that pertain to the device in the 510(k).

General Precautions:

- Never reuse this solution.

- Keep the bottle tightly closed when not in use.

Special Storage Conditions.

- Use before the expiration date marked on the [carton] [bottle] and [label] (use applicable).
- Keep out of the reach of children.
- Store at room temperature (if applicable).

Specific Precautions:

Daily Cleaners:

- Lenses should never be placed directly in the eyes from the cleaning solution. Always rinse and disinfect lenses after cleaning.

Periodic Cleaners:

- Tablets are not to be taken internally. If accidentally swallowed, [describe what may occur and measures to be taken].
- DO NOT use tablets that are broken or discolored.
- DO NOT use tablets from packages that are torn or punctured.
- Use only the special vials recommended for use with [TN].
- Use only freshly prepared enzymatic cleaning solution and discard immediately after use.
- DO NOT soak lenses for more than XX hours because [state reason as determined by test data (if applicable)].
- The enzymatic cleaning cycle is not a substitute for regular cleaning or disinfecting of your contact lenses.

Chemical Disinfecting Solutions/Systems:

Hydrogen Peroxide Systems:

- DO NOT USE OVER-THE-COUNTER GENERIC HYDROGEN PEROXIDE because [state reason].

Neutralizing Products:

- DO NOT use tablets that appear to be broken, chipped, or discolored.
- DO NOT use tablets from packages which are torn or punctured.

- DO NOT substitute [TN] Neutralizer components;
- DO NOT use neutralizing tablets in a heat disinfection unit.

In-Eye Contact Lens Solutions (Lubricating/Rewetting Drops):

- Add precautions that are specific to the device in the 510(k).

ADVERSE REACTIONS (Problems and what to do):

Adverse reactions include undesirable effects, reasonably associated with the use of the device, that may occur as part of the effect of the device or may be unpredictable in their occurrence.

[Include the following, as applicable to the device in the 510(k).]

The following problems may occur: eyes sting, burn or itch(irritation), comfort is less than when lens was first placed on the eye, feeling of something in the eye (foreign body, scratched area), excessive watering (tearing) of the eye, unusual eye secretions, redness of the eye, reduced sharpness of vision (poor visual acuity), blurred vision, rainbows or halos around objects, sensitivity to light (photophobia), or dry eyes.

If you notice any of the above:

IMMEDIATELY REMOVE YOUR LENSES.

- If the discomfort or problem stops, then look closely at the lens.
- If the lens is in any way damaged, DO NOT put the lens back on your eye. Place the lens in the storage case and contact your eye care practitioner.
- If the lens has dirt, an eyelash, or other foreign body on it, or the problem stops and the lens appears undamaged, thoroughly clean, rinse and disinfect the lens, then reinsert it.
- If the problem continues, IMMEDIATELY remove the lens and consult your eye care practitioner.

If any of the above symptoms occur, a serious condition such as infection, corneal ulcer, neovascularization or iritis may be present. Seek immediate professional identification of the problem and prompt treatment to avoid serious eye damage.

All adverse reactions observed while using [TN] should be reported to:

Name of Company
Address



1-800-[phone number]



[Insert information from predicate device labeling and any other information that is specific to the device in the 510(k).]

DIRECTIONS FOR USE:

General Instructions:

Always wash and rinse your hands before handling your lenses. This will help to prevent eye infections by removing dirt and oils that could get on the lenses.

Use only the solutions recommended by your eye care practitioner. Seek advice from your eye care practitioner before making any changes to your care regimen to ensure compatibility with lenses.

Always follow the directions for use in the labeling included with each solution as instructions may be different for each solution.

Specific Instructions: [Include specific Directions for Use (e.g., directions for a disinfecting regimen should describe all steps in the regimen using non-descriptive headings such as Step 1, Step 2, Step 3...), Directions for a disinfecting product (stand-alone) may describe the specific steps in the regimen using descriptive headings (e.g., Cleaning, Disinfection, Rinsing...)]

HOW SUPPLIED:

[Describe how device is packaged for distribution (e.g., quantity of contents, sterile, packaged in bottle/aerosol can, and marked with lot number and expiration date).]

MANUFACTURER OR DISTRIBUTOR NAME AND ADDRESS:

Include the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code.

Printed [Month and Year]

Note:

MULTI-PURPOSE SOLUTIONS

Labeling for multi-purpose solutions should combine the Description, Actions, Indications (Uses), Precautions, Warnings, and Directions for Use statements for each applicable indication (e.g., saline, disinfecting solution, cleaner). Duplicate words or phrases can be eliminated so that the resulting information is clear and understandable. Strict attention should be paid to the labeling for this product to assure that adequate directions for use (e.g., rubbing and rinsing times for daily cleaning, soak times for disinfection, and maximum storage times following disinfection) are provided for all intended uses identified above. A contact lens solution that cannot perform all of the functions indicated in the labeling should not be labeled as a multi-purpose contact lens care solution.

APPENDIX A (CONTINUED)

Bottle/Can Label:

Front:

- Product Trade Name
- Actions and Indications (e.g., cleans, disinfects, etc.)*
- Lens Statement [i.e., the type of lenses for which the device may be used (e.g., RGP or soft (hydrophilic) lenses)]
- Net Quantity Contents**
- Sterile

Side or Back:

- [Date Opened_____/or Discard Date_____] (when applicable)•Tamper-Resistant Statement***
- Description (i.e., Contents)
- SEE PACKAGE INSERT FOR... IMPORTANT SAFETY INFORMATION.
- Directions for Use
- Special Storage Conditions (e.g., store at room temperature)
- Keep out of Reach of Children
- Product Specific Warnings
- Insert the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot Number
- Expiration Date

* 21 CFR 801.61
 ** 21 CFR 801.62
 *** 21 CFR 800.12

APPENDIX A (CONTINUED)

Carton:

Principal Display Panel*:

- Product Trade Name
- Actions and Indications** (e.g., cleans, disinfects, etc.)
- Lens Statement (i.e., the type of lenses for which the device may be used)
- Net Quantity Contents***
- Sterile

Outer Carton Panels:

- Description (i.e., Contents)
- Contraindications:
 - If you are allergic to any ingredient in this device, DO NOT use.
 - Any additional known contraindications for specific device.
- Directions for Use (or reference Package Insert)
- Special Storage Conditions (e.g., store at room temperature)
- SEE PACKAGE INSERT FOR... IMPORTANT SAFETY INFORMATION.
- Keep out of Reach of Children
- Tamper-Resistant Statement****
- Product Specific Warnings
- Insert the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot Number
- Expiration Date

* 21 CFR 801.60
 ** 21 CFR 801.61
 *** 21 CFR 801.62
 **** 21 CFR 800.12

APPENDIX A (CONTINUED)

Package Insert Using Write-it-Right Principles

Included below is an example of a package insert for aerosol saline solution. This example incorporates principles taken from labeling entitled, "Improved Patient Instructions for Care of Soft Contact Lenses," that was prepared by a CDRH focus group based upon a study using consumers and Write-It-Right principles. This example differs somewhat in format from predicate device package inserts in that some sections have been rearranged, while others have been combined in an effort to eliminate duplication. In writing this package insert, icons were used to focus on various information. Warnings and precautions were boxed and strategically placed throughout the package insert to highlight the consumer's awareness to special considerations. Applicants developing new labeling or needing to bring their labeling up to date may choose to follow this sample package insert format or follow the format in predicate device labeling.

SAMPLE PACKAGE INSERT FOR MULTI-DOSE UNPRESERVED SALINE
(packaged in aerosol container)

IMPORTANT: Please read carefully and keep this information for future use.

[Trade Name (TN)]

WARNING

Serious injury to the eye and loss of vision may result from problems with contact lenses and lens care solutions. Eye problems, including corneal ulcers and infections, can develop rapidly. Immediately remove your lenses and call or visit your eye care practitioner if you experience any adverse reactions such as: eye discomfort, excessive tearing, vision changes, pain, unusual eye discharge, sensitivity to light, or redness of the eye.

[Note: Use only those indications included in the labeling that have been approved in a PMA or cleared in a 510(k).]

INDICATIONS/ACTIONS:

[TN] saline is indicated for use with (specify type) contact lenses for rinsing after cleaning to remove loosened debris and cleaning solution, rinsing prior to lens insertion, keeping lenses wet during heat disinfection, storage after disinfection, as a diluent for dissolving lens care tablets (e.g., enzyme or disinfecting tablets), and as a diluent for use in hydrogen peroxide disinfection systems (limited use).

DIRECTIONS FOR USE:**General Instructions:**

Always wash and rinse your hands before handling your lenses. This will help to prevent eye infections by removing dirt and oils that could get on the lenses.

Use only the solutions recommended by your eye care practitioner. Seek advice from your eye care practitioner before making any changes to your care regimen to ensure compatibility with lenses.

Always follow the directions for use in the labeling included with each solution as instructions may be different for each solution.

WARNING

To avoid contaminating your solution or your lenses:

- DO NOT transfer this solution into other bottles or containers.
- DO NOT touch nozzle tip of the can to any surface.

STEP 1. RINSE**WARNING**

- Contents under pressure, DO NOT spray directly into the eye, as serious injury to the eye may result.
- Always spray a small amount into the sink to clear the nozzle of contaminants before spraying the saline onto your lenses.



Rinse the lens thoroughly with fresh saline solution. Direct a stream of saline on both sides of the lens for at least 10 seconds.

STEP 2. HEAT DISINFECTION

Place each lens in the appropriate chamber of the storage case.



Fill each chamber with enough [TN] to completely cover the lenses.



Close the lens case tightly so that the lens will not dry out.



Place the lens storage case in your heat disinfection unit.



Follow the instructions that come with your heat disinfection unit.



Keep the lenses in the unopened lens case until you are ready to wear them.

CAUTION

- Never reuse the solution
- Store at room temperature
- Keep out of reach of children
- Use before expiration date marked on the container

WARNING

- To minimize the risk of contamination, DO NOT store lenses in saline that has not been heat disinfected.

WARNING CONTENTS UNDER PRESSURE

- DO NOT puncture or incinerate can.
- DO NOT store at temperatures above 120°F.

NOTE: This product may be used to dissolve enzyme tablets or as a neutralizing solution in some hydrogen peroxide systems. Follow the Directions for Use in the labeling accompanying your enzyme tablets or hydrogen peroxide system.

All contact lens wearers should see their eye care practitioner as often as directed. If your lenses are for extended wear, your eye care practitioner may prescribe more frequent visits to carefully monitor your ocular health.

DESCRIPTION/CONTENTS:

[TN] is a sterile isotonic [the following as applicable: buffered/unpreserved] solution containing [list all ingredients including any propellant(s)].

CONTRAINDICATIONS:

There are no known contraindications for use of this product OR

If you are allergic to any ingredient in [TN], DO NOT use.

ADVERSE REACTIONS:

All adverse reactions observed while using [TN] should be reported to:

Name of Company
Address



1-800-[phone number]



HOW SUPPLIED:

[TN] is supplied sterile in [] fl. oz. aerosol cans. Each can is marked with the lot number and expiration date.

Insert the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code

Printed [Month and Year]

LABELING--APPENDIX B

Lens Cases

[Include applicable information under the following headings. Applicants should use predicate device labeling as guidance].

TRADE NAME:

INDICATIONS: For storage of [soft (hydrophilic)/rigid gas permeable/and hard] contact lenses during [heat disinfection/heat or chemical disinfection (use applicable)].

Include additional limiting information (if applicable):

- For storage only - not for use as a container for heat or chemical disinfection.
- Use for storage during chemical disinfection only. DO NOT USE WITH HEAT.

DIRECTIONS FOR USE:

General Instructions: [Include preparing the lens case for use and how to care for the lens case daily.]

Specific Instructions: [Include step-by-step instructions for use.]

WARNINGS:

Warning for All Lens Cases:

- Lens cases can be a significant source of microbial contamination. To help prevent eye infections, lens cases should be cleaned, rinsed and air dried every day; and replaced frequently (as recommended by the manufacturer).

Warning for Lens Cases Indicated for Use in Chemical Disinfection Only:

- Use of this lens case with heat may cause warpage. USE FOR STORAGE DURING CHEMICAL DISINFECTION ONLY. DO NOT USE WITH HEAT.

ENDING:

- Include the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot No.
- Printed [Month and Year]

LABELING--APPENDIX C

Heat Disinfection Units

Applicants should follow the format of predicate device labeling for heat disinfection units.

The heat disinfection unit labeling should comply with 21 CFR 801.15, "Medical devices; prominence of required label statements," and 21 CFR 801.60, "Principal display panel."

Heat disinfection labeling should contain explanatory labeling of the heat indicator function. Listed below are models of what should be minimal acceptable labeling pertaining to indicator and heater function for contact lens heat disinfection units that utilize either a thermostat or electronic timer to automatically control the disinfection cycle. The applicant should pick the appropriate indicator information and integrate it into the labeling.

Alternate wording may be used, but the meaning of all labeling statements should be unchanged. Emphasis shown in the model labeling by use of uppercase lettering is considered to be essential. Both carton and user instruction paragraphs should be located and emphasized by use of bold faced type or contrasting color so as to elicit the attention of the user.

1. MODEL LABELING FOR UNITS WITH LIGHT FOR POSITIVE FUNCTION/FAILURE INDICATOR

Package Labeling:

Principal Display Panel:

HEATER INDICATOR LIGHT - This unit uses a light to indicate the start and finish of the disinfection cycle.

READ USER INSTRUCTIONS CAREFULLY

Any Panel:

THE UNIT HAS A LIGHT TO INDICATE THE START AND FINISH OF THE DISINFECTION CYCLE THAT ONLY LIGHTS WHEN THE HEATER IS ON. ALLOW ____ MINUTES COOLING TIME AFTER THE LIGHT GOES OFF BEFORE REMOVING LENSES.

User Instructions:

CAUTION: Observe the light indicator to confirm that the unit is operating correctly. It must turn on when the unit is started and turn off after ____ to ____ minutes. REPLACE THE UNIT if the light does not turn on when the unit is started or does not turn off within ____ minutes after being started.

2. MODEL LABELING FOR UNITS WITH A TEMPERATURE SENSOR (NON-LIGHT) INDICATOR FOR POSITIVE FUNCTION/FAILURE INDICATOR

Package Labeling:

Principal Display Panel:

HEAT SENSOR - This unit uses a heat sensor to indicate the start and finish of the disinfection cycle by (describe how).

READ USER INSTRUCTIONS CAREFULLY

Any Panel:

THE UNIT HAS A HEAT SENSITIVE INDICATOR THAT TELLS WHEN DISINFECTION STARTS BY CHANGING FROM _____ TO _____ AND TELLS WHEN THE UNIT IS COOL ENOUGH TO REMOVE LENSES SAFELY BY CHANGING FROM _____ TO _____.

User Instructions:

CAUTION: Observe the heat sensor to confirm that the unit is operating correctly. It must change from ____ to ____ after starting the disinfection cycle. Observe the heat sensor again after completion of the disinfection cycle and prior to unplugging the unit. It must change back from ____ to _____. REPLACE THE UNIT if the heat sensor does not change.

Carton Label:

TRADE NAME:

INDICATIONS:

DIRECTIONS FOR USE:

Before First Use: [Provide necessary instructions.]

Heat (Thermal) Disinfection: [Provide step-by-step instructions for disinfecting lenses.]

Maintenance of Your Heat Disinfection Unit [Provide necessary maintenance instructions.]

CONTRAINDICATIONS: [DO NOT use with rigid gas permeable or hard contact lenses.]

WARNINGS:

General Warnings:

- DO NOT IMMERSE OR RINSE UNIT IN TAP WATER. IF SALINE, WATER, OR OTHER LIQUIDS COME IN CONTACT WITH THE EXTERIOR OF THE UNIT, _____, AND _____, IMMEDIATELY WIPE DRY BEFORE USING.
- [Include other general warnings as applicable.]

Warnings for Electrical Device (as applicable):

SAVE THESE INSTRUCTIONS:

To reduce the risk of electrocution:

- DO NOT operate your [TN] if the unit is wet. Dry exterior surfaces before using.
- DO NOT touch the [TN] or the removable electrical plug with wet hands.
- Always unplug this product immediately after using.
- DO NOT use while bathing.
- DO NOT place or store product where it can fall or be pulled into a bath or sink.
- DO NOT place in or drop into water or other liquid.

To reduce the risk of burns, electrocution, fire or injury:

- Close supervision is necessary when this product is used by, on, or near children or invalids. This is not a toy for children.
- Never operate this product if it has a damaged cord or plug, if it is not working properly, if it has been dropped or damaged, or dropped into water.
- DO NOT use outdoors or operate where aerosol products are being used or where oxygen is being administered.
- Electrical shock can occur if the unit is wet or if the electrical plug is not completely engaged in the receptacle.

DESCRIPTION: [Include description of device, including indicator and how it works.]

ENDING: Include the information that expresses the facts:

- [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot or Serial No.
- Printed [Month and Year]

LABELING--APPENDIX D

Salt Tablets/Capsules Systems:

On September 21, 1987, CDRH sent a letter to salt tablet PMA owners and interested persons advising them that specific directions for use and warnings should be used in salt tablet labeling to ensure safe and effective use of homemade saline from salt tablets. PMA owners subsequently revised their labeling in accordance with CDRH's letter. No changes have been made in CDRH's policy since the September 21 letter issued. The letter advised PMA owners that CDRH believes that there is sufficient scientific evidence to demonstrate that (1) salt tablets/capsules saline should NOT be used in conjunction with chemical disinfection systems for contact lens care and (2) the continued use of salt tablets/capsules saline in conjunction with heat disinfection requires greater consumer awareness that salt tablets/capsules saline should NEVER be used FOLLOWING heat disinfection. The letter further stated that the following labeling (Warnings and Indications for Use) should be used for salt tablets/capsules system labeling to provide continuing safety and effectiveness of the device for its intended use. All labeling for salt tablets/capsules systems should follow the format of predicate device labeling that has been revised after the September 21, 1987 letter issued and include the information listed below:

1. Carton Labeling

The front panel of the salt tablets/capsules carton should prominently display the following warning:

WARNING: USE THIS PRODUCT EXACTLY AS DIRECTED. The package insert for this product contains WARNINGS and SAFETY INFORMATION. PLEASE READ IT CAREFULLY.

2. INDICATIONS: The Indications for Use statement should read as follows:

For rinsing and for use during heat disinfection and storage of soft (hydrophilic) contact lenses.

Rinsing PRIOR to heat disinfection only.

Storage DURING heat disinfection only.

3. Package Insert

General Warning Statements - The package insert for this product should prominently display the following warnings:

SALT TABLETS/CAPSULES

WARNINGS: AN ASSOCIATION HAS BEEN ESTABLISHED BETWEEN IMPROPER USE OF SALT TABLETS/CAPSULES SALINE AND SERIOUS EYE INFECTIONS THAT MAY RESULT IN LOSS OF SIGHT.

DISTILLED WATER IS A NON-STERILE PRODUCT. THE USE OF NON-STERILE PRODUCTS IN THE PREPARATION OF CONTACT LENS

SOLUTIONS MAY LEAD TO CONTAMINATION OF LENSES BY MICROORGANISMS INCLUDING ACANTHAMOEBA WHICH CAN CAUSE SERIOUS EYE INFECTIONS AND RESULT IN PERMANENT VISUAL LOSS.

WHILE CHEMICAL DISINFECTION SOLUTIONS, INCLUDING HYDROGEN PEROXIDE, ARE EFFECTIVE IN KILLING MICROORGANISMS THAT COMMONLY PRODUCE EYE INFECTIONS, THEY MAY NOT BE EFFECTIVE AGAINST THE ACANTHAMOEBA ORGANISM. FOLLOW THESE REVISED INSTRUCTIONS CAREFULLY, OR DISCONTINUE USE OF SALT TABLETS/CAPSULES SALINE.

- NEVER USE SALT TABLETS/CAPSULES SALINE SOLUTION WITH CHEMICAL OR HYDROGEN PEROXIDE DISINFECTION OF CONTACT LENSES.
- NEVER USE SALT TABLETS/CAPSULES SALINE SOLUTION AS A RINSE AFTER ANY DISINFECTION (use only a commercially prepared sterile saline solution for rinsing after disinfection).
- NEVER USE SALT TABLETS/CAPSULES SALINE SOLUTION DIRECTLY IN THE EYE.

DIRECTIONS FOR USE:

DESCRIPTION/CONTENTS:

PRECAUTIONS:

CONTRAINDICATIONS:

ADVERSE REACTIONS:

HOW SUPPLIED:

ENDING:

- Insert the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot Number
- Expiration Date
- Printed [Month and Year]

LABELING--APPENDIX E

Contact Lens Accessories (Mechanical Cleaning Aids)

[Include applicable information under the following headings. Applicants should use predicate device labeling as guidance].

TRADE NAME:

INDICATIONS/ACTIONS: [Include specific indications (e.g., [TN] is indicated for use with contact lens cleaning solutions to aid in cleaning by minimizing hand contact with lenses.)]

CONTRAINDICATIONS: [If there are no known contraindications, add the statement: "There are no known contraindications associated with the use of this device." If there are contraindications, list them.]

DIRECTIONS FOR USE: [Include step-by-step directions for use including what products can be used with the device.]

WARNINGS: [Include warnings applicable to the device in the 510(k).]

Warnings for Electrical Device: [Include the information from the labeling example for Heat Disinfection Units (Labeling--Appendix C), if applicable].

PRECAUTIONS:

- To avoid damage to lenses, follow precautions in the contact lens solution labeling.
- [Additional precautions specific to the device in the 510(k).]

ADVERSE REACTIONS:

ENDING:

- Include the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot or Serial No.
- Printed [Month and Year]

LABELING--APPENDIX F

Contact Lens Accessories (Accessory Cleaning Pads)

[Include applicable information under the following headings. Applicants should use predicate device labeling as guidance].

TRADE NAME:

INDICATIONS/ACTIONS: [Include specific indications (e.g., [TN] is indicated for use with contact lens cleaning solutions to aid in cleaning by minimizing hand contact with lenses).]

CONTRAINDICATIONS: [If there are no known contraindications, add the statement: "There are no known contraindications associated with the use of this device." If there are contraindications, list them.]

DIRECTIONS FOR USE: [Include step-by-step directions for use, including how to clean the pad, and how often to replace it.]

WARNINGS:

- [Add for pads that are to be reused.] To help avoid contamination and eye infection, clean and air-dry pad every day; replace pad every (insert number) day(s).
- [Add for pads that are disposable (i.e., use once and throw away).] To help avoid contamination and eye infection, discard pad after each use.
- [Additional warnings applicable to the device in the 510(k).]

PRECAUTIONS:

- To avoid damage to lenses, use exactly as instructed in the contact lens solution labeling.
- [Additional precautions specific to the device in the 510(k).]

ADVERSE REACTIONS:

ENDING:

- Include the information that expresses the facts: [Distributed by/Manufactured by/Manufactured for] Address including zip code
- Lot No.
- Printed [Month and Year]

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INTRODUCTION

This section of the guidance includes recommended preclinical and clinical test methods designed to provide data to assess substantial equivalence of contact lens care products to legally marketed devices. Whenever possible, the guidance references applicable standards that have been finalized and have been found acceptable for use by CDRH.

CDRH is actively working on the development of contact lens product standards with the American National Standards Institute (ANSI) and the International Organization of Standards (ISO) in an effort to harmonize our requirements and recommended test methods with voluntary standards being developed nationally and internationally. Although some contact lens care product standards have been completed and published for use, a number of important standards are currently under development and have not been completed or adopted at this time. For those standards currently under development, CDRH has attempted to harmonize our requirements and recommended test methods, to the extent possible, with standards being drafted at this time. For purposes of harmonization, elements of those draft standards that CDRH finds acceptable have been incorporated into the appropriate sections of this guidance or into the recommended test methods included in this section.

CHEM--APPENDIX A**PRESERVATIVE UPTAKE/RELEASE TEST PROCEDURES**

The purpose of this test is to determine preservative uptake/release in solutions containing new preservatives for contact lens use. The results of these test data will be used to predict the potential for a preservative related toxicity, as well as the potential for inducing a sensitivity/allergic response associated with the contact lens care products.

The test procedures outlined here have been accepted by CDRH for the quantitative analysis of the uptake/release of preservatives, such as thimerosal, chlorhexidine, and benzalkonium chloride, in contact lenses. It is the responsibility of the applicant to select a validated chemical method for the quantitative analysis of the uptake/release of the preservative from the lens, whether it be thimerosal, chlorhexidine, benzalkonium chloride or other newer agents.

In general, a thermodynamically defined "plateau" of total* accumulation of preservative on the lens should be demonstrated for the recommended lens care regimen. Alternatively, the preservative uptake/release studies through equilibration studies can substitute cycling studies (e.g., each lens is soaked in 100 ml care solution at room temperature for 4 days, 8 days, and 12 days or longer).

At least three data points, each separated by at least 20 cycles under the recommended lens care regimen, should be submitted. Each data point should be expressed in terms of the average value, standard deviation, and number of measurements. A statistical analysis should be performed to ensure that it reaches a plateau area. For hydrophilic contact lenses, it should be expressed as μg preservative/mg dry lens; however, for hydrophobic contact lenses, it should be expressed as μg preservative/surface area of lens in cm^2 .

A. Thimerosal Uptake/Release Studies of Hydrophilic and Hydrophobic Lens Materials by Atomic Absorption Spectrometry:

1. Sample Preparations

Each lens, after cycling under the recommended care regimen or after a reasonable soaking time in the thimerosal preserved care solution, is placed in a borosilicate vial and bathed in 1 ml isotonic pH = 7.0 buffered saline solution at 35°C for 15 hours (preservative release study). The lens is removed from the vial, blot-dried, and placed in another borosilicate vial which is used for the preservative uptake study.

2. Preservative Uptake Study

Five ml of concentrated sulfuric:nitric acid (3:1 by volume**) are added to the vial containing the lens. The vial is heated, gently

*Total accumulation of preservative on the lens is a sum of preservative uptake and preservative release data.

**2:1 by volume for hydrophilic plastic lenses.

at first on a hot plate until the lens is decomposed. Care should be taken during heating to avoid charring. The vial is then heated strongly to remove all traces of nitric acid, which is determined visually by the presence of white vapor instead of brown vapor (nitrous oxide) inside the vial. If charring occurs, a few drops of concentrated nitric acid are added and the sample reheated.

The entire sample is employed for the mercury determination using cold vapor atomic absorption spectrometry. Two control lenses, which have been soaked in an isotonic pH = 7.0 buffered saline solution for the duration of the study (35°C for 15 hours), are decomposed and treated as the test lens. Absorbance values for the sample lenses are corrected by subtracting the absorbance value of the control lens.

3. Preservative Release Study

Five ml of concentrated sulfuric:nitric acid (3:1 by volume**) are added to the vial containing lens leachate. The solution is treated as the test lens. A control solution (an isotonic pH = 7.0 buffered saline solution) is also treated as the test lens. Absorbance values for the lens leachates are corrected by subtracting the absorbance value of the control solution.

4. Standard Curve

Five ml of concentrated sulfuric:nitric acid (3:1 by volume**) are added to the vial containing a known concentration of thimerosal standard. The standard solution is treated as the test lens. A reagent blank (concentrated sulfuric:nitric acid = 3:1 by volume) is also treated as the test lens. Absorbance values for the standard solutions are corrected by subtracting the absorbance value of the reagent blank.

B. Chlorhexidine Uptake/Release Studies of Hydrophilic and Hydrophobic Lens Materials by ¹⁴C-Labeled Technique:

The procedure for chlorhexidine (CHG) can be used for any preservative which can be tagged with a non-labile radioactive label.

CHG accumulation by contact lenses is assessed by ¹⁴C counting of radiolabeled CHG associated with the lens after the recommended care regimen. The modified procedure of MacKeen and Green*** specifically designed for preservative determination in contact lenses is briefly described as follows:

***MacKeen, D.L. and Green, K.: Chlorhexidine Kinetics of Hydrophilic Contact Lenses; J. Pharm. Pharmacol., 30: 578-682, 1978.
MacKeen, D.L. and Green, K.: Chlorhexidine Kinetics in Hard Contact Lenses; J. Pharm. Pharmacol., 31: 714-716, 1979.

1. Sample Preparations

Radiolabeled ^{14}C -CHG is added to the care solution containing CHG.

Each lens after cycling under the recommended care regimen containing ^{14}C -CHG or after a reasonable soaking time in ^{14}C -CHG preserved care solution is placed in a scintillation vial and bathed in 1 ml isotonic pH = 7.0 buffered saline solution at 35°C for 15 hours (preservative release study). The lens is removed from the vial, blot-dried, and placed in another scintillation vial which is used for the preservative uptake study.

2. Preservative Uptake Study

Three ml of concentrated sulfuric:nitric acid (3:1 by volume**) are added to the vial containing the lens. The vial is heated to boiling. After cooling to room temperature, duplicate 100 μl samples are taken of the resultant solution, mixed with 1 ml of deionized water and 10 ml of Aquasol (New England Nuclear Corporation) with vigorous agitation. After cooling, the samples are counted. The control lens, just removed from the shipping container, is solubilized and treated as the test lens. The counts for the test lenses are corrected by subtracting the counts of the control lens.

3. Preservative Release Study

Three ml of concentrated sulfuric:nitric acid (3:1 by volume**) are added to the vial containing lens leachate. The vial is heated to boiling. After cooling to room temperature, duplicate 100 μl are mixed with 1 ml of deionized water and 10 ml of Aquasol and counted. Duplicate 100 μl of a control solution (an isotonic pH = 7.0 buffered saline solution) are also treated in the same way. The counts for lens leachate are corrected by subtracting the counts of the control solution.

4. Standard

Three ml of concentrated sulfuric:nitric acid (3:1 by volume**) are added to the scintillation vial containing 100 μl of ^{14}C -CHG standard solution. The vial is heated to boiling. After cooling to room temperature, duplicate 100 μl samples are taken of the resultant solution, mixed with 1 ml deionized water and 10 ml of Aquasol with vigorous agitation. After cooling, the samples are counted.

- C. Chlorhexidine Uptake/Release Studies of Hydrophilic Lens Materials by High Pressure Liquid Chromatography (HPLC)

This procedure for chlorhexidine uptake/release studies can be used for hydrophilic lens materials which show a strong absorption and adsorption to CHG through electrostatic interactions.

The modified procedure of Stevens et al⁺ specifically designed for preservative determination in hydrophilic lens materials is briefly described as follows.

Lenses are soaked in a minimum volume of care solution at room temperature for 4 days, 8 days, and 12 days or longer. The CHG accumulation by hydrophilic lens materials is assessed by a difference in concentrations of CHG in the care solution before and after lens soaking. After soaking, the lens is removed and placed in 1 ml isotonic pH = 7.0 buffered solution at 35°C for 15 hours (preservative release study). The CHG concentrations in both soaking and elution solutions are determined by injecting sample aliquots of 20 µl directly onto the HPLC column and calculating from the standard. The detection limit, reproducibility, and reliability should be assessed compared to preservative uptake/release studies to ensure the suitability of this method.

D. Benzalkonium Chloride (BAK) Uptake/Release Studies of Hydrophobic Lens Materials by Laser Fluorescence Spectroscopy++

1. Sample Preparation

After cycling under the recommended care regimen or after a reasonable soaking time in BAK preserved care solution, each lens is placed in a vial and bathed in 1 ml isotonic pH = 7.0 buffered saline solution at 35°C for 15 hours (preservative release study). The lens that is removed from the vial and air-dried is used for the preservative uptake study.

2. Preservative Uptake Study

Adsorbed BAK is measured by laser fluorescence spectroscopy with an argon laser. The excitation intensity is on the order of 4×10^{-6} Einsteins/second, providing a fluorescence spectrum level of 10^3 counts/second at the phototube. For detection, a Hamamatsu photomultiplier tube biased with a Keithley microammeter/high voltage power is used. Monochromators are double JY 0.5 meter holographic gratings.

3. Preservative Release Study

Total adsorbed BAK on the lens is also measured by laser fluorescence spectroscopy. The difference between total adsorbed BAK and adsorbed BAK is the value for preservative release study.

+Stevens, L.E., Durrwachter, J.R., and Helton, D.O.: Analysis of Chlorhexidine Sorption in Soft Contact Lenses by Catalytic Oxidation of ¹⁴C-Chlorhexidine and by Liquid Chromatography: J. Pharm. Sci., 75: 83-86, 1986.

++Wong, M.P., Dziabo, A.J., and Kiral, R.M.: Dynamics of BAK Adsorption by Silicone Acrylate Lenses; Contact Lens Spectrum, November. 49-53, 1986.

CHEM--APPENDIX B**CLEANING EFFECTIVENESS****Determination of the Critical Micelle Concentration of a Surfactant (or Surfactant System) in a Lens Care Product Having a Cleaning Claim**

In an aqueous solution of a surfactant, the surfactant is molecularly dispersed at low concentrations. At higher concentrations, however, when a certain critical concentration is reached, the molecules form micelles. These micelles are in equilibrium with the free surfactant molecules. The concentration that must be reached in order that micelles are formed is called the critical micelle concentration. Adequate cleaning effectiveness of a daily cleaner can be demonstrated in vitro by determining that the concentration of a surfactant (or surfactants) in a daily cleaner are higher than the critical micelle concentration of surfactant (or surfactants).

Many physical properties of the surfactant solution when plotted against the concentration show more or less sudden changes at the critical micelle concentration. By measuring such properties as electrical conductivity, interfacial tension, surface tension, refractive index, viscosity, and light scattering as a function of the concentration of the surfactant, the critical micelle concentration is determined as the concentration at which the property versus concentration curve shows a change in slope. The hydrophobic part of the surfactant molecule is situated at the inside of the micelle, the hydrophilic part at the outside. Inside the micelles lipophilic substances may be solubilized.

The purpose of a daily cleaner is to remove loosely held lens deposits on the lens surface. Generally, a daily cleaner contains at least a surfactant which lowers surface tension of the solution to facilitate removal of loosely held lens deposits on the lens surface in conjunction with mechanical means (e.g., fingers). The concentration of a surfactant (or surfactants) in a daily cleaner should be sufficient enough to be higher than the critical micelle concentration of surfactant (or surfactants). The critical micelle concentration of surfactant may be significantly affected by pH, tonicity, and other inactive ingredients in the daily cleaner.

The purpose of this appendix is not intended to list all methods to determine the critical micelle concentration of surfactant (or surfactants). Rather, we are providing a simple method such as measuring surface tension of a surfactant (or surfactants) in a device medium to determine the critical micelle concentration.

1. Solution 1: Prepare the daily cleaner medium (i.e., the daily cleaner without surfactants).
2. Solution 2: Prepare a reasonable concentration of the surfactant system (if more than one surfactant is in the daily cleaner, the weight or mole ratio of the surfactant system should be the same as the one in the daily cleaner).
3. Solution 3: Prepare varying concentrations of the surfactant system in the daily cleaner medium by diluting Solution 2 with Solution 1.

4. Measure surface tension of Solution 3 by the Tensiometer.
5. Plot surface tension versus log concentration of surfactant system in the daily cleaner medium (Solution 3) and perform least square linear regressions to determine the critical micelle concentration.

CHEM--APPENDIX C**SOLUTION COMPATIBILITY TEST PROTOCOL**

The purpose of this test is to assess the effect of a contact lens solution on contact lens parameters and solution compatibility under the recommended care regimen. CDRH does not believe that data will ordinarily be required to be submitted in the 510(k) if the solution is essentially identical to the predicate device in terms of active and inactive ingredients. For purpose of this guidance, our focus is on active ingredients. However, manufacturers should also assess the effects of inactive ingredients on such factors as pH and tonicity, which could significantly affect solution compatibility. For hydrophilic contact lenses, CDRH considers tinted contact lenses to represent the worst case. The following is a suggested protocol:

1. Number of Cycles:

30 cycles for heat disinfection regimen
30 cycles for chemical or hydrogen peroxide disinfection regimen

2. Number of Lenses:

For hydrophilic contact lenses

Group I: at least 10 lenses with low powers

Group IV: at least 10 lenses with low powers

For hydrophobic contact lenses

Number of lenses should be equally divided between the lens groups for which the solution is indicated, for a total of 20 lenses

3. Parameters Monitored:

Optical parameters: power, base curve, and diameter

Physical appearance: discoloration and clarity

Chemical parameters: tint (if applicable)

ultraviolet absorption (if applicable)

4. Test Method:

- a. Record optical, physical, and chemical parameters before cycling.
- b. Flex lenses in a manner to simulate removal of the lens from the eye (not applicable for hydrophobic lenses).
- c. Clean, rinse, and disinfect lenses (including handling procedures) as required in the labeling for the recommended care regimen.
- d. Repeat (b) if applicable and (c) for each cycle up to 30 cycles with the appropriate heat disinfection, chemical disinfection, and hydrogen peroxide regimen.
- e. Record optical, physical, and chemical parameters after cycling.
- f. Summarize and discuss the test results.

MICRO--APPENDIX A

PRESERVATIVE EFFICACY OF MULTI-DOSE
PRESERVED CONTACT LENS CARE PRODUCTSI. PRINCIPLE

The antimicrobial activity test uses a standard inoculum of a representative range of microorganisms to challenge a preserved product and establishes the extent of viability loss at predetermined time intervals. The size of the microbial challenge chosen in this test is not intended to be representative of the likely challenge in practice but to provide countable numbers from which estimation of the rate and extent of viability loss can be determined. The capability of the product to prevent microbial growth is evaluated.

In carrying out the test for antimicrobial activity the qualitative and quantitative composition of the product at the time of testing should be known by either analytical testing or extrapolation.

Appropriate measures should be taken to inactivate or remove residual antimicrobial agents during recovery of survivors, and the effectiveness of these measures should be demonstrated.

Three lots of product should be tested. Each lot of product should be tested with a separate inoculum preparation for each challenge organism.

II. MATERIALS & REAGENTS

A. Test Organisms

Pseudomonas aeruginosa	NCIMB 8626	ATCC 9027
Staphylococcus aureus	NCTC 10788	ATCC 6538
Escherichia coli	NCIB 8245	ATCC 8739
Candida albicans	NCPF 3179	ATCC 10231
Aspergillus niger	IMI 149007	ATCC 16404

B. Test Media

Tryptone Soya Broth (TSB), Tryptone Soya Agar (TSA), Sabouraud Dextrose Agar (SDA), Dulbecco's Phosphate Buffered Saline without calcium chloride and magnesium chloride (DPBS): 200 mg/l KCl, 200 mg/l KH_2PO_4 , 8000 mg/l NaCl, and 2,160 mg/l $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ or suitable diluent; Dulbecco's Phosphate Buffered Saline plus 0.05% w/v polysorbate 80 (DPBST) or suitable diluent
Validated neutralizing agents/media as required (e.g., Dey-Engley Neutralizing Broth and Agar).

C. Test Equipment

Sterile pipettes, glass beads, swabs, tubes, 100 X 20 mm petri dishes, etc., as required. Suitable instruments for spectrophotometric determination of cell density, for colony counting, and for centrifugation.

D. Test Samples

Product samples to be tested should be representative of the product to be marketed. Aliquots should be taken directly from the final product container immediately prior to testing.

III. TEST METHOD

A. Culture Maintenance

Cultures should be maintained in the manner recommended by the curator of the appropriate culture collection. Cultures should be no greater than 5 passes removed from the depository stock (ATCC, NCIB, NCTC, NCPF or other recognized culture depository).

B. Preparation of Microbial Challenge (Inoculum)

Test organisms should be cultured on agar as in Table 1.

Table 1: Media & Incubation Conditions for Growth of Challenge Organisms

Organism	Medium	Incubation	
		Temp °C	Time
<i>Pseudomonas aeruginosa</i>	TSA	30-35	18-24h
<i>Staphylococcus aureus</i>	TSA	30-35	18-24h
<i>Escherichia coli</i>	TSA	30-35	18-24h
<i>Candida albicans</i>	SDA	20-25	42-48 or
	SDA	30-35	18-24h
<i>Aspergillus niger</i>	SDA	20-25	7 days

To harvest all cultures, use sterile DPBST or a suitable diluent, washing the surface growth and transfer to a suitable vessel. The spore suspensions may be filtered through sterile glass wool, cotton gauze, or cheese cloth to remove hyphal fragments.

After harvesting, the cultured organisms may be washed using centrifugation. If centrifugation is used, each centrifugation should be conducted at 2-25°C for no longer than 10 minutes at 4000 x g or less. The bacterial suspensions may be filtered (e.g., 3 - 5 µm pore size) to produce a single cell dispersion.

All challenge cell suspensions should then be adjusted with DPBST or other suitable diluent to 1×10^7 - 1×10^8 colony forming units (cfu)/ml. The approximate cell concentration may be estimated by measuring the turbidity of the suspension or a

dilution of the suspension using a spectrophotometer. The actual concentration of cfu/ml should be determined for each suspension by the plate count method at the time of the test.

Bacterial and yeast cell suspensions should be used on the day of preparation. Bacterial and yeast cells may lose viability and resistance if not used on the day of preparation. Spore suspensions may be used up to 7 days following preparation by storage under refrigeration (Avg. $4 \pm 2^\circ\text{C}$).

C. Test Procedure

1. Prepare one tube containing a minimum of 10 ml of test solution per challenge organism. Inoculate the sample tube of the product to be tested with a suspension of test organisms sufficient to provide a final count of 1.0×10^5 - 1.0×10^6 cfu/ml. The volume of inoculum should not exceed 1% of the sample volume. Ensure dispersion of the inoculum by adequate mixing.
2. Store inoculated product at $20-25^\circ\text{C}$. Temperature should be monitored using a calibrated device and documented. If sensitive to light the product should be protected during the period of the test.
3. Take 1.0 ml aliquots of the inoculated product for determination of viable count at 7 days and 14 days.
4. Each sample is rechallenged as in III.C.1 on day 14 after taking the 14-day sample. Use an inoculum level of 1.0×10^4 - 1.0×10^5 cfu/ml.
5. Take 1.0 ml aliquots of the inoculated product for determination of viable count at 21 and 28 days.
6. Subject 1.0 ml aliquots removed at the specified time intervals to a suitable series of decimal dilutions in validated neutralizing media. Mix suspension well by vortexing vigorously and incubate for a suitable period of time to allow for neutralization.

If the antimicrobial agent(s) in the formulation cannot be adequately inactivated or neutralized it may be eliminated using a validated membrane filtration procedure (Micro--Appendix D).

7. Determine the viable count of organisms in appropriate dilutions by preparation of triplicate plates (unless otherwise justified) of suitable recovery medium (e.g., TSA for bacteria and SDA for mold and yeast). The agar for pour plates should be kept between $40-50^\circ\text{C}$ prior to pouring. The agar media used for determination of viable counts may also contain antimicrobial inactivators or neutralizers if required. Where membrane filtration has been employed to remove/neutralize antimicrobial agents, membranes should be cultured on these media as appropriate.

8. Incubate bacterial recovery plates at 30-35°C for 2-4 days. Incubate yeast at 20-25°C or 30-35°C for 3-5 days and mold recovery plates at 20-25°C for 3-7 days.
9. Determine the average number of cfu on countable plates and record. Countable plates refer to 30-300 cfu/plate for bacteria and yeast, and 8-80 cfu/plate for mold except when colonies are observed only for 10^0 or 10^{-1} dilution plates. Calculate microbial reduction at the specified time points.
10. The concentration of survivors is calculated at each time point. The concentration of viable organisms following the 14-day rechallenge is the sum of the rechallenge inoculum concentration and the 14-day survivor concentration.

D. Controls

1. Inoculum Controls

The initial and rechallenge inoculum concentrations are calculated by dispersing an identical aliquot of the inoculum into the same volume of a suitable diluent (e.g., DPBST) as used in III.C.1 to achieve a final concentration of 1.0×10^5 - 1.0×10^6 cfu/ml for the initial inoculum or 1.0×10^4 - 1.0×10^5 cfu/ml for the rechallenge inoculum. Ensure dispersion of the inoculum by adequate mixing. This control sample should be evaluated within 1 hour of its preparation using the same procedure used for the inoculated product. This serves to demonstrate the suitability of the medium used for growth of the test organism and provides an estimate of the initial (rechallenge) inoculum concentration.

2. Recovery Medium Control

Qualify the neutralizing agent/medium for the product initially and periodically thereafter. Prepare a 1/10 dilution of the preserved product in the validated neutralizing broth (1 ml into 9 ml). If a greater dilution of the test solution is required to achieve neutralization, the latter dilution should be used. Prepare a second control tube with 10 ml of a suitable diluent (e.g., TSB). Inoculate the tubes with sufficient inoculum to result in 10 - 100 cfu of challenge organism per plate. Incubate for an appropriate period of time at ambient temperature. Plate the appropriate aliquot from each tube onto the recovery agar plates in triplicate unless otherwise justified. The recovery in the neutralizer broth should be at least 50% of the recovery in the second control tube. This control is to be performed for each challenge organism.

IV. PERFORMANCE CRITERIA

A. Bacteria

The number of organisms recovered per ml is reduced by a mean value of not less than 3.0 logs at 14 days. After the rechallenge at day 14, the concentration of bacteria should be reduced by at least a mean value of 3.0 logs by day 28.

B. Molds and Yeasts

The number of organisms recovered per ml remain at or below the initial concentrations within an experimental error of ± 0.5 logs within 14 days. At day 28, the concentration of mold and yeast should remain at or below the concentrations after the rechallenge within an experimental error of ± 0.5 logs.

C. Products should be capable of meeting these criteria throughout their labeled shelf-life.

MICRO--APPENDIX B

DISINFECTION EFFICACY TESTING

PART 1. STAND-ALONE PROCEDURE FOR DISINFECTING PRODUCTS

I. PRINCIPLE

The stand-alone test challenges a disinfecting product with a standard inoculum of a representative range of microorganisms and establishes the extent of viability loss at pre-determined time intervals comparable with those during which the product may be used. The size of the microbial challenge chosen in this test is not intended to be representative of the likely challenge in practice, but to provide countable numbers from which estimation of the rate and extent of viability loss can be determined.

In carrying out the test for antimicrobial activity, the qualitative composition of the product should be known at the time of testing by either analytical testing or extrapolation.

Appropriate measures should be taken to inactivate or remove residual antimicrobial agents during culturing and counting of survivors and the effectiveness of these measures should be validated and the action of this process during the test should be demonstrated by the construction of suitable controls.

Three batches of product should be tested. Each batch of product should be tested with a separate inoculum preparation for each challenge organism.

II. MATERIALS AND REAGENTS

A. Test Organisms

<i>Pseudomonas aeruginosa</i>	NCIMB 8626	ATCC 9027
<i>Staphylococcus aureus</i>	NCTC 10788	ATCC 6538
<i>Serratia marcescens</i>	NCTC 10211	ATCC 13880
<i>Candida albicans</i>	NCTC 3179	ATCC 10231
<i>Fusarium solani</i>		ATCC 36031

B. Test Media

Potato Dextrose Agar (PDA)
 Tryptone Soya Broth (TSB)
 Tryptone Soya Agar (TSA)
 Sabouraud Dextrose Agar (SDA)
 Dulbecco's Phosphate Buffered Saline without calcium chloride and magnesium chloride (DPBS): 200 mg/L KCl, 200 mg/L KH₂PO₄, 8000 mg/L NaCl, and 2,160 mg/L Na₂HPO₄•7H₂O or a suitable diluent.
 Dulbecco's Phosphate Buffered Saline plus 0.05% w/v polysorbate 80 (DPBST) or a suitable diluent.
 Validated neutralizing agents/media required (e.g., Dey-Engley Neutralizing Broth and Agar).

C. Test Equipment

Sterile pipettes, glass beads, swabs, tubes, 100 X 20 mm petri dishes, etc., as required. Suitable instruments for spectrophotometric determination of cell density, for colony counting, and for centrifugation.

D. Test Samples

Product samples to be tested should be representative of the product to be marketed. Aliquots should be taken directly from the final product container immediately prior to testing.

III. TEST METHOD

A. Culture Maintenance

Cultures should be maintained in the manner recommended by the curator of the appropriate culture collection. Cultures should be no greater than five passes removed from the depository stock (ATCC, NCIB, NCTC, NCPF or other recognized culture depository.)

B. Preparation of Microbial Challenge (Inoculum)

Test organisms should be cultured on agar as in Table 1.

Table 1

Media and Incubation Conditions for Growth of Challenge Organisms

Organism	Medium	Temp(°C)	Incubation Time
P. aeruginosa	TSA	30-35	18-24 hrs
S. aureus	TSA	30-35	18-24 hrs
S. marcescens	TSA	30-35	18-24 hrs
C. albicans	SDA	20-25	42-48 hrs or
	SDA	30-35	18-24 hrs
F. solani	PDA	20-25	10-14 days

To harvest all cultures, use sterile DPBST or a suitable diluent, washing the surface growth and transfer to a suitable vessel. The spore suspensions may be filtered through sterile glass wool, cotton gauze or cheese cloth to remove hyphal fragments.

After harvesting, the cultured organisms may be washed using centrifugation. If centrifugation is used, each centrifugation should be conducted at 2-25°C for no longer than 10 minutes at 4000 x g or less. The bacterial suspensions may be filtered (e.g., 3 - 5 µm pore size) to produce a single cell dispersion. All challenge cell suspensions should then be adjusted with DPBST or other suitable diluent to 1×10^7 - 10^8 cfu/ml. The approximate cell concentration may be estimated by measuring the turbidity of the suspension or a dilution of the suspension using a spectrophotometer. The actual concentration of cfu/ml should be determined for each suspension by the plate count method at the time of the test.

Bacterial and yeast cell suspensions should be used on the day of preparation. Bacterial and yeast cell may lose viability and resistance if not used on day of preparation. Spore suspensions may be used up to 7 days following preparation by storage under refrigeration (Avg. $4 \pm 2^{\circ}\text{C}$).

C. Test Procedure

1. Prepare one tube containing a minimum of 10 ml of test solution per challenge organism. Inoculate the sample tube of the product to be tested with a suspension of test organisms sufficient to provide a final count of 1.0×10^5 - 1.0×10^6 cfu/ml. The volume of inoculum should not exceed 1% of the sample volume. Ensure dispersion of the inoculum by adequate mixing.
2. Store inoculated product at $20-25^{\circ}\text{C}$. Temperature should be monitored using a calibrated device and documented. If sensitive to light the product should be protected during the period of the test.
3. Take 1.0 ml aliquots of the inoculated product for determination of viable count at 25%, 50%, 75% and 100% of the minimum recommended disinfection time for all organisms, and, in addition, at not less than 4 times the minimum recommended disinfection time for yeast and mold. Where overnight disinfection is recommended, disinfection time is taken to be 8 hours.
4. Subject 1.0 ml aliquots removed at the specified time intervals to a suitable series of decimal dilutions in validated neutralizing media. Mix suspension well by vortexing vigorously and incubate for a suitable period of time to allow for neutralization.

If the antimicrobial agent(s) in the formulation cannot be adequately inactivated or neutralized it may be eliminated using a validated membrane filtration procedure (e.g., Micro--Appendix D).

5. Determine the viable count of organisms in appropriate dilutions by preparation of triplicate plates (unless otherwise justified) of a suitable recovery medium (e.g., TSA for bacteria and SDA for mold and yeast).

Where membrane filtration has been employed to remove/neutralize antimicrobial agents, membranes should be cultured on these media as appropriate. The agar for pour plates should be kept between $40-50^{\circ}\text{C}$ prior to pouring. The agar media used for determination of viable counts may also contain antimicrobial inactivators or neutralizers if required.

6. Incubate bacterial recovery plates at $30-35^{\circ}\text{C}$ for 2-4 days. Incubate yeast at $20-25^{\circ}\text{C}$ or $30-35^{\circ}\text{C}$ for 3-5 days and mold recovery plates at $20-25^{\circ}\text{C}$ for 3-7 days.

7. Determine the average number of cfu on countable plates. Countable plates refer to 30 to 300 cfu/plate for bacteria and yeast, and 8 to 80 cfu/plate for mold except when colonies are observed only for the 10^0 or 10^{-1} dilution plates. Calculate microbial reduction at the specified time points.

D. Controls

1. Inoculum Control

An inoculum count is made by dispersing an identical aliquot of the inoculum into the same volume of suitable diluent (e.g., DPBST) as used in Part 1:III.C.1 to achieve a final concentration of 1.0×10^5 - 1.0×10^6 cfu/ml. The volume of inoculum should not exceed 1% of the sample volume. Ensure dispersion of the inoculum by adequate mixing. This control sample should be evaluated for cfu/ml at the beginning of the test. This serves to demonstrate the suitability of the medium used for growth of the test organism and provides an estimate of the initial inoculum concentration.

2. Recovery medium control

Prepare a 1/10 dilution of the disinfecting solution in the validated neutralizing broth (1 ml into 9 ml). If a greater dilution of the test solution is required to achieve neutralization, the latter dilution should be used. Prepare a second control tube with 10 ml of a suitable diluent (e.g., TSB). Inoculate the tubes with sufficient inoculum to result in 10-100 cfu of challenge organism per plate. Incubate for an appropriate period of time at ambient temperature. Plate the appropriate aliquot from each tube onto the recovery agar plates in triplicate unless otherwise justified.

The recovery in the neutralizer broth should be at least 50% of the recovery in the second control tube. This control should be performed for each challenge organism.

IV. PERFORMANCE REQUIREMENT

A. Control Specification

If any control value falls out of specification, the associated test is invalid and should be repeated.

B. Primary Criteria (See Part 2, Table 2)

1. Bacteria

The number of organisms recovered per ml should be reduced by a mean value of not less than 3.0 logs within the minimum recommended disinfection period.

2. Molds and Yeasts

The number of organisms recovered per ml should be reduced by a mean value of not less than 1.0 log within the minimum recommended disinfection time with no increase at not less than four times the minimum recommended disinfection time.

C. Secondary Criteria (See Part 2, Table 2)

Products failing to meet the criteria in Part I:IV.B.1 or Part 1:IV.B.2 may be evaluated by the regimen test procedure described below, provided there is a combined log reduction for the means of all bacteria of not less than 5.0 within the recommended disinfection period. The minimum acceptable mean log reduction for any single bacterial type is 1.0. Stasis for the yeast and mold (within an experimental error of +0.5 log) should be observed for the recommended disinfection period.

PART 2. REGIMEN PROCEDURE FOR DISINFECTING REGIMENS**I. PRINCIPLE**

This procedure is applicable to multi-functional disinfection regimens which may include the steps of cleaning, rinsing, and soaking. In carrying out the regimen test procedure, the products should be used in the manner and quantity recommended in product labeling and/or patient instructions. The test challenges the proposed disinfection regimen with a standard inoculum of a representative range of microorganisms. The inoculum is carried through the various stages of the regimen by preliminary application to contact lenses.

The disinfecting stage of any proposed contact lens disinfection regimen evaluated by this test should have demonstrated minimum antimicrobial activity by the Stand-Alone Procedure as indicated for Regimen Qualification.

In carrying out the test, qualitative and quantitative composition of all products used in the test regimen should be known at the time of testing, either by analytical testing or extrapolation.

Appropriate measures should be taken to inactivate or remove residual antimicrobial agents during culturing and counting of the challenge organism and the effectiveness of these measures should be demonstrated by the construction of suitable controls.

A minimum of three lots of product should be tested. Each lot of product should be tested with a separate inoculum preparation for each challenge organism.

II. MATERIALS AND REAGENTS**A. Test Organisms**

Pseudomonas aeruginosa	NCIMB	8626	ATCC 9027
Staphylococcus aureus	NCTC	10788	ATCC 6538
Serratia marcescens	NCTC	10211	ATCC 13880
Candida albicans	NCPF	3179	ATCC 10231
Fusarium solani			ATCC 36031

B. Test Media

Tryptone Soya Broth (TSB)
 Tryptone Soya Agar (TSA)
 Sabouraud Dextrose Agar (SDA)
 Potato-Dextrose Agar (PDA)
 Dulbecco's Phosphate Buffered Saline without calcium chloride and magnesium chloride (DPBS): 200 mg/L KCl, 200 mg/L KH_2PO_4 , 8000 mg/L NaCl, and 2,160 mg/L $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ or suitable diluent.
 Dulbecco's Phosphate Buffered Saline plus 0.05% w/v polysorbate 80 (DPBST) or suitable diluent. Validated neutralizing agents/media as required (e.g., Dey-Engley Neutralizing Broth and Agar).

C. Test Equipment

Sterile pipettes, glass beads, swabs, tubes, filters, etc., as required. Suitable instruments for spectrophotometric determination of cell density, for colony counting, and for centrifugation.

D. Test Samples

Test product samples to be tested should be representative of the product to be marketed. Aliquots should be taken directly from the final product container immediately prior to testing. All regimen items, including cases, lenses, cleaning devices, etc., should be new and unused. If the test regimen results will be directly compared with results for a predicate device, then a predicate device from the same product category should be used for the comparison (e.g., a hydrogen peroxide product should be compared to a predicate hydrogen peroxide system and a multi-purpose product should be compared to a predicate multi-purpose product). Refer to Part 2:IV (PERFORMANCE REQUIREMENT).

III. TEST METHODS

A. Culture Maintenance

Cultures should be maintained in the manner recommended by the curator of the appropriate culture collection. Cultures should be no greater than 5 passes removed from the depository stock (ATCC, NCIB, NCTC, NCPF or other recognized culture depository).

B. Preparation of Microbial Challenge (Inoculum)

Test organisms should be cultured and harvested as in Part 1:III.B.

After harvesting, organic soil consisting of heat killed yeast cells and heat inactivated serum, should be combined with the test organism to result in an initial concentration of $1 \times 10^7 - 10^8$ cfu/ml.

Prepare organic soil as follows. Culture *S. cerevisiae* on SDA at 20-25°C for 48 hrs. Harvest as in Part 1:III.B. Heat kill the suspension at 100 ±2°C for 10 minutes. Centrifuge at no more than 5000 X g for a maximum of 30 minutes. Resuspend in bovine serum which has been heated at 56°C for 30 minutes to inactivate complement. The concentration of *S. cerevisiae* in serum should be $1 \times 10^7 - 10^8$.

Centrifuge test organism suspension. Resuspend in organic soil to a concentration $1 \times 10^7 - 10^8$ cfu/ml. This is the inoculum to be used in the following procedure.

C. Test Procedure

1. Lens Inoculation

The test should be conducted with lens types representative of those with which the regimen is intended to be used (e.g., low water non-ionic, high water ionic, silicone acrylate, etc.).

Inoculate eight lenses per lot of test product per microbial species tested; to qualify for all hydrophilic lenses use four (4) non-ionic low water lenses and four (4) ionic high water lenses. For hydrophobic lenses, use four (4) silicone-acrylate and four (4) fluorosilicone-acrylate lenses.

Organism 1	<u>Hydrophilic Lenses</u>	
	Group I Material	Group IV Material
Lot 1 of Test Product	4 lenses	4 lenses
Lot 2 of Test Product	4 lenses	4 lenses
Lot 3 of Test Product	4 lenses	4 lenses
	<u>12 lenses</u>	<u>12 lenses</u>
Organism 1	<u>Hydrophobic Lenses</u>	
	Silicone-Acrylate	Fluorosilicone-Acrylate
Lot 1 of Test Product	4 lenses	4 lenses
Lot 2 of Test Product	4 lenses	4 lenses
Lot 3 of Test Product	4 lenses	4 lenses
	<u>12 lenses</u>	<u>12 lenses</u>

For hydrophilic or hydrophobic lenses, a total of 120 lenses (24 for each organism/60 lenses in each representative lens material) will be needed to test all 5 organisms.

Place test and control lenses, concave surface uppermost in a sterile petri dish.

Inoculate each lens by placing 0.01 ml of inoculum on the under surface of the lens at the point of contact between the petri dish and the lens, and 0.01 ml of inoculum on the top surface of the lens.

Allow the inoculum to absorb to each lens for 5-10 min. at 20-25°C.

2. Lens Treatment

After inoculum absorption, treat lenses as described in the manufacturer's consumer instructions for lens disinfection, including all steps of cleaning, rinsing and soaking specified by the manufacturer. Cleaning and rinsing

procedures (e.g., rubbing and rinsing times and rinse volumes) should be performed in identical fashion for the predicate device and the test sample, unless otherwise stated in the manufacturer's consumer instructions for lens care. Test protocols should specify these parameters.

3. Recovery of Surviving Challenge Organisms (e.g., Micro--Appendix D Membrane Filtration Procedure)
 - a. Dispense suitable volume of validated neutralizing medium into filtration apparatus.
 - b. Transfer entire content of each test lens case (lens and solution) into the neutralizing medium in the filtration apparatus. The neutralization exposure time prior to filtration should be determined in the validation study.
 - c. Apply vacuum and filter solution. Rinse the filter two additional times with the neutralizing medium.
 - d. Aseptically transfer the lens onto a bed of agar medium appropriate for recovery of the test organism. Pour 40-50⁰C agar medium (same as bed agar above) over the lens to cast it.
 - e. Apply the test filter to the surface of a plate of appropriate solid media (could be the same as used in Part 2:III.C.3.d).
 - f. Incubate bacterial recovery plates at 30-35⁰C for 2-4 days. Incubate yeast recovery plates at 20-25⁰C or 30-35⁰C for 3-5 days and mold recovery plates at 20-25⁰C for 3-7 days.

D. Controls

1. Lens Inoculation Control

For each microbial species tested transfer 3 inoculated lenses to tubes of TSB (for bacteria and yeasts) or SDB (for fungi) as appropriate. Vortex for 30 seconds. Serially dilute and plate out appropriate dilutions to permit a count of viable cells present.

This count confirms that the number of organisms on the lens at the time of regimen challenge is adequate. The mean of the 3 counts should be not less than 2.0×10^5 .

2. Neutralization and Recovery Control

Prepare filtration apparatus in triplicate (unless otherwise justified) as in Part 2:III.C.3 with suitable volumes of neutralizing medium and disinfecting solution. Add 5 to 50 cfu of challenge organism, filter and cultivate as outlined in Part 2:III.C.3.

Confirm inoculum on suitable medium in triplicate unless otherwise justified.

The recovery in the neutralizer broth should be at least 50% of the inoculum.

IV. PERFORMANCE REQUIREMENT

Bacteria, molds and yeast (See Table 2)

Less than or equal to 10 cfu recovered from each lens and test filter combination for each test organism. Alternatively, the average number of surviving organisms recovered on the lens and the respective test filter should be shown to be substantially equivalent to results obtained for the predicate device(s) when tested according to this regimen procedure. Organism counts (average for each organism) may be considered to be substantially equivalent if the difference between the subject device and the predicate device is less than or equal to 0.5 log.

Table 2

SUMMARY OF RECOMMENDED PERFORMANCE
CRITERIA FOR CONTACT LENS DISINFECTION PROCEDURES

PRODUCT	MEAN LOG REDUCTION AT DISINFECTION TIME				
	FUNGI		BACTERIA		
	FS ^a	CA	SM	PA	SA
Stand-Alone Criteria	1	1	3	3	3
Regimen Qualification	b	b	c	c	c
Regimen Criteria	d	d	d	d	d

- a FS = *F. solani* ATCC 36031,
CA = *C. albicans* ATCC 10231,
SM = *S. marcescens* ATCC 13880,
PA = *P. aeruginosa* ATCC 9027,
SA = *S. aureus* ATCC 6538

- b Stasis with an experimental error of ± 0.5 log at the disinfection time.

- c The minimum acceptable log reduction for the mean value of all 3 bacteria combined should be 5.0. The minimum acceptable log reduction for any single bacterial type should be 1.0.

- d Less than or equal to 10 cfu per lens and test filter combination from 0.01 ml of 1×10^7 to 1×10^8 inoculum OR

The average combined number of surviving organisms recovered on the lens and the respective test filter must be shown to be substantially equivalent to the predicate device(s).

MICRO--APPENDIX C**BACTERIOSTASIS TEST****I. PRINCIPLE**

Bacteriostasis testing is performed for multi-dose saline products which do not contain conventional preservatives, yet do contain bacteriostatic agents (e.g., borate, boric acid, potassium sorbate, and EDTA). For these products, which do not meet the preservative efficacy criteria described in Micro--Appendix A, a discard date should be determined on the basis of the product's bacteriostatic activity. The bacteriostasis test is a modification of the preservative efficacy test procedure.

Three lots of product should be tested. Each lot of product should be tested with a separate inoculum preparation for each challenge organism.

II. MATERIALS & REAGENTS**A. Test Organisms**

<i>Pseudomonas aeruginosa</i>	NCIMB 8626	ATCC 9027
<i>Staphylococcus aureus</i>	NCTC 10788	ATCC 6538
<i>Escherichia coli</i>	NCIB 8245	ATCC 8739
<i>Candida albicans</i>	NCPF 3179	ATCC 10231
<i>Aspergillus niger</i>	IMI 149007	ATCC 16404

B. Test Media

Tryptone Soya Broth (TSB), Tryptone Soya Agar (TSA), Sabouraud Dextrose Agar (SDA), Dulbecco's Phosphate Buffered Saline without calcium chloride and magnesium chloride (DPBS): 200 mg/l KCl, 200 mg/l KH_2PO_4 , 8000 mg/l NaCl, and 2,160 mg/l $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ or suitable diluent

Dulbecco's Phosphate Buffered Saline plus 0.05% w/v polysorbate 80 (DPBST) or suitable diluent

Validated neutralizing agents/media as required (e.g., Dey-Engley Neutralizing Broth and Agar).

C. Test Equipment

Sterile pipettes, glass beads, swabs, tubes, 100 X 20 mm petri dishes, etc., as required. Suitable instruments for spectrophotometric determination of cell density, for colony counting, and for centrifugation.

D. Test Samples

Product samples to be tested should be representative of the product to be marketed. Prepare one tube containing a minimum of 10 ml of test solution per challenge organism. The largest container size proposed for the product should be used.

III. TEST METHOD

A. Culture Maintenance

Cultures should be maintained in the manner recommended by the curator of the appropriate culture collection. Cultures should be no greater than 5 passes removed from the depository stock (ATCC, NCIB, NCTC, NCPF or other recognized culture depository).

B. Preparation of Microbial Challenge (Inoculum)

Test organisms should be cultured on agar as in Table 1.

Table 1: Media & Incubation Conditions for Growth of Challenge Organisms

Organism	Medium	Incubation	
		Temp °C	Time
<i>Pseudomonas aeruginosa</i>	TSA	30-35	18-24h
<i>Staphylococcus aureus</i>	TSA	30-35	18-24h
<i>Escherichia coli</i>	TSA	30-35	18-24h
<i>Candida albicans</i>	SDA	20-25	42-48 or
	SDA	30-35	18-24h
<i>Aspergillus niger</i>	SDA	20-25	7 days

To harvest all cultures, use sterile DPBST or a suitable diluent, washing the surface growth and transfer to a suitable vessel. The spore suspensions may be filtered through sterile glass wool, cotton gauze or cheese cloth to remove hyphal fragments.

After harvesting, the cultured organisms may be washed using centrifugation. If centrifugation is used, each centrifugation should be conducted at 2-25°C for no longer than 10 minutes at 4000 x g or less. The bacterial suspensions may be filtered (e.g., 3 - 5 µm pore size) to produce a single cell dispersion. All challenge cell suspensions should then be adjusted with DPBST or other suitable diluent to 1×10^7 - 1×10^8 cfu/ml or cell concentration sufficient to result in final concentration of 1×10^5 - 1×10^6 cfu/ml in the product. The approximate cell concentration may be estimated by measuring the turbidity of the suspension or a dilution of the suspension using a spectrophotometer. The actual concentration of cfu/ml should be determined for each suspension by the plate count method at the time of the test.

Bacterial and yeast cell suspensions should be used on the day of preparation. Bacterial and yeast cells may lose viability and resistance if not used on the day of preparation. Spore suspensions may be used up to 7 days following preparation by storage under refrigeration (Avg. $4 \pm 2^\circ\text{C}$).

C. Test Procedure

1. Inoculate the sample product to be tested with a suspension of test organisms sufficient to provide a final count of 1.0×10^5 - 1.0×10^6 cfu/ml. The volume of inoculum should not exceed 1% of the sample volume. Ensure dispersion of the inoculum by adequate mixing.
2. Store inoculated product at 20-25°C. Temperature should be monitored using a calibrated device and documented. If sensitive to light the product should be protected during the period of the test.
3. Take 1.0 ml aliquots of the inoculated product for determination of viable count at 7, 14, 21, and 28 days. If longer discard dates are desired, continue sampling periodically thereafter.
4. Subject 1.0 ml aliquots removed at the specified time intervals to a suitable series of decimal dilutions in validated neutralizing media. Mix suspension well by vortexing vigorously and incubate for a suitable period of time to allow for neutralization.

If the antimicrobial agent(s) in the formulation cannot be adequately inactivated or neutralized it may be eliminated using a validated membrane filtration procedure (e.g., Micro-Appendix D).

5. Determine the viable count of organisms in appropriate dilutions by preparation of triplicate plates (unless otherwise justified) of suitable recovery medium (e.g., TSA for bacteria and SDA for mold and yeast). The agar for pour plates should be kept between 40-50°C prior to pouring. The agar media used for determination of viable counts may also contain antimicrobial inactivators or neutralizers if required. Where membrane filtration has been employed to remove/neutralize antimicrobial agents, membranes should be cultured on these media as appropriate.
6. Incubate bacterial recovery plates at 30-35°C for 2-4 days. Incubate yeast at 20-25°C or 30-35°C for 3-5 days and mold recovery plates at 20-25°C for 3-7 days.
7. Determine the average number of cfu on countable plates and record. Countable plates refer to 30-300 cfu/plate for bacteria and yeast, and 8-80 cfu/plate for mold except when colonies are observed only for 10^0 or 10^{-1} dilution plates. Calculate microbial reduction at the specified time points.
8. The concentration of survivors should be calculated at each time point.

D. Controls

1. Inoculum Controls

The initial inoculum concentration should be calculated by dispersing an identical aliquot of the inoculum into the same volume of a suitable diluent (e.g., DPBST) as used in III.C.1 to achieve a final concentration of 1.0×10^5 - 1.0×10^6 cfu/ml. Ensure dispersion of the inoculum by adequate mixing. This control sample should be evaluated at the same time as the zero time sample. This serves to demonstrate the suitability of the medium used for growth of the test organism and provides an estimate of the initial inoculum concentration.

2. Recovery Medium Control

Qualify the neutralizing agent/medium for the product initially and periodically thereafter. Prepare a 1/10 dilution of the product in the validated neutralizing broth (1 ml into 9 ml). If a greater dilution of the test solution is required to achieve neutralization, the latter dilution should be used. Prepare a second control tube with 10 ml of a suitable diluent (e.g., TSB). Inoculate the tubes with sufficient inoculum to result in 10 - 100 cfu of challenge organism per plate. Incubate for an appropriate period of time at ambient temperature. Plate the appropriate aliquot from each tube onto the recovery agar plates in triplicate unless otherwise justified. The recovery in the neutralizer broth should be at least 50% of the recovery in the second control tube. This control is to be performed for each challenge organism.

IV. PERFORMANCE CRITERIA

A. Bacteria

The concentration of each bacterial challenge organism should remain at the initial level or decrease.

B. Molds and Yeasts

The concentration of the yeast and mold should remain at initial levels or decrease within an experimental error of ± 0.5 log.

C. The product should be labeled to discard the container after it has been opened for the number of days which corresponds to time point previous to the point at which any organism shows an increase in number (see example). The container label should include a space on which to record the date opened.

Example:

(Concentration in Abbreviated Log Value)

	0	7	DAY 14	21	28	35
E. coli	10^5	10^3	<10	10^1	10^2	10^3
P. aeru.	10^5	10^3	10^3	10^2	10^3	10^4
S. aureus	10^5	<10	<10	<10	<10	<10
C. alb.	10^5	10^5	10^4	10^2	<10	<10
A. niger	10^5	10^4	10^3	10^4	10^4	10^5

Cut off point:	E. coli	14 days
	P. aeru.	21 days
	A. niger	14 days

The use of the above hypothetical product is limited to 14 days after opening.

MICRO--APPENDIX D

MEMBRANE FILTRATION PROCEDURE

I. SUMMARY

This document provides an example of procedures and controls for membrane filtration.

II. MATERIALS AND REAGENTS

A. Test Media

Suitable diluent with or without neutralizers
Tryptone Soya Agar (TSA)
Sabouraud Dextrose Agar (SDA)
Dulbecco's Phosphate Buffered Saline without calcium chloride and magnesium chloride (DPBS): 200 mg/L KCl, 200 mg/L KH_2PO_4 , 8000 mg/L NaCl, and 2,160 mg/L $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ or other suitable diluent
Dulbecco's Phosphate Buffered Saline plus 0.05% w/v polysorbate 80 (DPBST)

B. Test Equipment

Sterile pipettes, petri dishes, containers, etc., as needed.
Suitable sterile apparatus for holding the sterile membrane filter and the filtrate. Suitable equipment for creating a vacuum or pressure to cause the liquid phase of the inoculated test solution to pass through the membrane filter aseptically. The membrane filter should have a nominal pore size of not greater than 0.45 μm , a diameter of at least 47 mm and should be free of chemicals which could be toxic to microbial cells.

III. TEST METHOD

- A. Moisten the sterile membrane filter in a sterile filter assembly with sterile DPBST or other suitable diluent.
- B. Aseptically transfer a measured volume of the inoculated test solution into sterile DPBST or other suitable diluent.
- C. Transfer the diluted solution to the membrane and filter immediately with the aid of vacuum or pressure. The sample applied to the filter should be diluted in 50-100 ml of dilution fluid and thoroughly mixed to ensure uniform distribution of the sample over the entire area of the filter. This will decrease the probability of multiple cfu being placed on the filter at the same location.
- D. Wash the membrane filter with several volumes of a suitable diluent which may contain additional neutralizing agents as needed. Three volumes of a suitable diluent (100 ml each) are usually sufficient to remove and/or dilute the antimicrobial agent. The actual volume should be determined empirically for each formulation for each challenge organism.

- E. The membrane filter is then aseptically incubated with appropriate media to allow growth of cfu on the surface of the filter. This may be accomplished by aseptic removal of the membrane filter from the filter assembly unit and placement of the membrane on the surface of a sterile agar plate which does not have obvious liquid on the surface or the membrane may be enclosed in an agar sandwich. Alternatively, a sterile membrane filter unit may be used which requires addition of sterile media to the sealed filter and incubation of the membrane in situ. Media should be used which are appropriate for the type of challenge organism and the specific formulation under test.
- F. Determine the average number of cfu on countable membrane filters (3-100 cfu/47 mm filter for bacteria and yeast and 3-10 cfu/47 mm filter for molds). Calculate the cfu/ml of inoculated solution.
- G. Controls

Neutralizer efficacy may be confirmed by transferring an aliquot of the uninoculated test solution into 50-100 ml of sterile diluting fluid using the same ratio of volume of test solution to volume of diluting fluid. Apply the entire volume to the membrane and filter using vacuum or pressure. Wash the filter with several volumes of the diluting fluid using the same volume as used for the test procedure. Transfer 10-20 cfu for bacteria and yeasts or 3-10 cfu for molds into 100 ml of diluting fluid and apply to the membrane. Incubate the membrane filter in contact with media as described in the test procedure (see section III.E).

The procedure should be repeated using diluting fluid not exposed to the test solution. Counts should be compared with those derived by the same method but using DPBST instead of test solution. The count observed for diluting fluid with test solution should be comparable with that obtained for diluting fluid. The latter count should be statistically comparable with a direct plate count on rich medium to eliminate the possibility of loss of viable cells by filtration or test medium toxicity.

TOXICOLOGY

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TOX--APPENDIX A

TOXICOLOGY

I. Introduction

This section of the guidance document discusses the toxicological considerations that CDRH believes should be addressed in order to assess substantial equivalence in terms of safety and biocompatibility of contact lens care products.

In an effort to harmonize the biological response to testing of medical devices, CDRH has issued blue book memorandum #G95-1 entitled "Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part-1: Evaluation and Testing," which includes an FDA-modified matrix that delineates the type of testing recommended for various medical devices. It also includes a flow chart entitled "Biocompatibility Flow Chart for the Selection of Toxicity Tests for 510(k)s." The tests recommended in this toxicology section are generally consistent with the studies recommended in the blue book memorandum but have been adapted for specific use with contact lens care products.

The manufacturing process and chemical formulation used to fabricate a contact lens/lens care product should dictate, in general, the extent of the toxicology testing necessary to establish substantial equivalence in terms of its safety and effectiveness. It is the applicant's responsibility to develop an appropriate toxicology and biocompatibility profile for the specific lens material/lens care product in order to demonstrate that the device is substantially equivalent in terms of safety and effectiveness to the predicate device. Any test suggested in this toxicology section may be replaced by a suitable alternative if the alternative test has been validated or can be justified for use as an alternative. All nonclinical laboratory studies should include a statement that each study was conducted in compliance with the GLP Regulation for Nonclinical Laboratory Studies. If the study was not conducted in compliance with the GLP Regulation, a justification of the noncompliance should be submitted.

CDRH is aware of the ongoing research efforts to achieve the goal of eventual substitution of in vitro tests for certain biological tests utilizing animals*. However, at present, in vitro alternatives to animal testing have not been sufficiently developed or validated for use. Therefore, CDRH regrets that toxicology tests involving animals will continue to be used at this time in order to adequately assess risks and evaluate safety of ocular products prior to 510(k) clearance. CDRH will continue to monitor the developments of alternatives to animal testing and will recommend their use once such studies have been validated.

*Goldberg, A.M., et al. Framework for Validation and Implementation of In Vitro Toxicity Test: Report of the Validation and Technology Transfer Committee of the Johns Hopkins Center for Alternatives to Animal Testing. J. Am. Coll. Tox. 1993: 12:23-30.

The toxicology studies recommended below are generally consistent with the applicable studies recommended in normative standards and/or USP/NF 23.

NOTE: In addition to the recommended tests listed, CDRH believes that the material safety data sheet (MSDS) should be submitted in order to establish a toxicology profile for active ingredients and/or new chemical components incorporated into the finished contact lens care product (i.e., preservative, tablet, etc.). CDRH is aware that additional safety and toxicology data are generally included in the MSDS which can be obtained from the supplier of the chemical constituent, in lieu of performing additional or repetitive toxicology testing. The MSDS should be included in the 510(k) submission.

II. Minimum Recommended Toxicology Test Procedures for Contact Lens Care Products (i.e., Solutions/Tablets)

A. In-Vitro Cytotoxicity, USP/NF 23

The purpose of this study is to evaluate the potential for toxicity of residual chemicals leaching from the lens into the care products (i.e., solution(s)/solubilized tablets). In addition, this test may be used to detect potential toxic carryover from uptake/release of the solution by the lens. The effects are assessed *in vitro* using cytotoxicity studies (i.e., Tissue Culture-Agar Diffusion Test, Direct Contact Test and/or Elution Test) or a suitable validated alternative method.

B. Acute Ocular Irritation, USP/NF XXII

The purpose of the study is to evaluate the potential for ocular irritation resulting from residual chemical leachables from the finished device which may be extracted in the care products (i.e., solution(s)/solubilized tablets). This method is also used to detect the potential for ocular irritation due to carryover from uptake/release of the solution by the lens and from direct instillation of an in-eye solution. This test should not be needed in cases where formulations contain known ocular irritants. In such cases, an appropriate warning should be required on the label for products known to cause ocular irritation (i.e., daily cleaners/periodic cleaners) in lieu of performing this test.

C. Acute Oral Toxicity

The purpose of this study is to assess the potential of the contact lens care product (i.e., solution(s)/tablet(s)) to produce a toxic response as a result of deliberate or accidental ingestion of the device by adults or children. These data will be used to determine the need for additional warnings or precautions in the labeling of the product for the purpose of consumer protection. For rodent testing, the maximum volume of an aqueous solution generally should not exceed 2 ml/100 g body weight. This single large dose is referred to as the maximum tolerable dose (MTD). However, should signs of toxicity be demonstrated at this MTD,

further testing consistent with accepted toxicological practices is recommended in order for CDRH to complete its risk/benefit assessment of the device. See Tox--Appendix B for the suggested test method.

III. Additional Recommended Testing

Data from the following tests should be submitted if a manufacturer is using a new preservative or an active ingredient/chemical component not previously used in a currently marketed contact lens care product.

A. Sensitization (Guinea Pig Maximization Test*):

The purpose of this test is to grade or rank chemical constituents on a scale of I through V as to their potential for inducing sensitivity response in the guinea pig model. The grades of rankings are based on the number of animals sensitized, and results are classified on an ascending scale from a weak sensitizing agent (grade I) to an extreme sensitizing agent (grade V).

*Magnusson, B. and Kligman, A.M. The Identification of Contact Allergens by Animal Assay. The Guinea Pig Maximization Test. J. Invest. Dermatol. 1969; 52.

B. In-Vivo Ocular Biocompatibility (ISO 9394-1994):

This test method entitled, "Optics and optical instruments--Determination of biological compatibility of contact lens material --Testing of the contact lens system by ocular study with rabbit eyes," is published as an international standard by ISO. This ISO standard has been evaluated by CDRH, and we believe it should be acceptable in its entirety to address preclinical ocular biocompatibility of contact lens products.

IV. Toxicology Tests for Containers

The purpose of these testing requirements is to indirectly or directly assess the potential toxicity of constituent(s) that may leach from the container when the solution comes in contact with the container for a prolonged period of time. The following in vitro and in vivo test procedures are recommended by CDRH and are consistent with the procedures listed in USP/NF XXII, Containers for Ophthalmics--Plastics (Biological Test Procedures).

A. Systemic Injection Test, USP/NF XXII

B. Acute Ocular Irritation

C. In-Vitro Cytotoxicity

TOX--APPENDIX B**ACUTE ORAL TOXICITY**

The following is a generalized test protocol that may be used as guidance in assessing a contact lens solution for acute oral toxicity. Specific test procedures may vary for each individual laboratory but generally should follow the outline given below.

Purpose of the Study:

The objective of the study is to evaluate the potential oral toxicity of a designated test material following a single oral dose at 15 g/kg of body weight.

This study should be conducted in accordance with the requirements of the Good Laboratory Practice (GLP) Regulations (21 CFR 58).

Control Article:

No control article should be employed in this study, since dose response during the study may serve as an internal control.

Test System and Justification:

Ten albino rats of the Sprague-Dawley strain (five male, five female), obtained from a commercial supplier, should be selected from the stock colony after a minimum 5-day acclimation period. Prior to overnight food deprivation, animal weights should range from 200 to 300 g. Rats should be identified by ear punch and housed, according to sex, up to five per suspended cage.

The rat has been historically used to establish relative LD₅₀ data. The oral route of dosing is selected as the strongest challenge for materials that could be accidentally ingested. A 15 g/kg dose is generally regarded as nontoxic (Gleason, et al, 1969).

Animal Management:

Animal husbandry and environmental conditions should conform to specifications based on the "Guide for the Care and Use of Laboratory Animals," National Institutes of Health (NIH) Publication No. 85-23. Rats should receive a commercial rodent food on a daily basis; tap water should be freely available.

No contaminants are suspected to be present in the food or water that would affect the results of this study.

No sedation, analgesia or anesthesia should be necessary in this procedure. In the unlikely event that an animal should become injured, ill, or moribund, euthanasia or veterinary care should be conducted in accordance with current veterinary medical practice.

Test Article Preparation:

Density (g/ml) of the liquid should be determined prior to dosing.

As far as practical, composition of the test substance should be known. Information should include the name and quantities of all major components, known contaminants and impurities, and the percentage of unidentifiable materials to account for 100% of the test substance. Ideally, the lot of the substances tested should be the same throughout the study. The test sample should be stored under conditions that maintain its stability, strength, quality, and purity from the date of its productions until the tests are complete.

Methods and Route of Administration:

Food should be withheld overnight (16-20 hours). Each rat should then be gavaged with a single 15 g/kg dose of the test material via stainless steel blunt tipped cannula attached to a disposable syringe. The maximum dose volume should not exceed 2 ml/100 g body weight. The rats should be weighed at dosing, at observation day 7, and at day 14 of the study. Animals should be observed for clinical signs of toxicity immediately after dosing, at 4 hours after dosing and daily for 14 days. Food should be returned following the immediate observation. Rats found dead during the study and those euthanatized should be subjected to a macroscopic examination of the viscera. A complete gross necropsy should be performed on all animals that die during the course of the study.

Evaluations and Statistics:

Mean body weights should be calculated for all animals at dosing (day 0) and for survivors at days 7 and 14. Statistical manipulation of data is not applicable to this study.

Should 80% of the animals survive, the test material preparation should not be considered orally toxic. Greater than 20% mortality may warrant additional investigation.

Report:

The report should contain a description of the methods employed, data accumulated in tabular form and a summary of results.

Quality Assurance:

Inspections should be conducted at the major phases of the study (e.g., test article preparation, dosing, and necropsy). The final report should also be inspected for conformance to Subpart J of the GLP Regulations (21 CFR 58.185). A Certificate of Quality Assurance Inspections should be provided with the final report.

Records:

Test article preparation, animal weights, observations for adverse clinical signs, macroscopic necropsy findings, and dates of relevant activities (e.g., study initiation and completion) should be recorded.

All raw data pertaining to this study and a copy of the final report should be retained in the designated archive files of the testing laboratory/sponsor.

References:

21 CFR 58 (GLP Regulations)

Gleason, M.N., et al. 1969. Clinical Toxicology of Commercial Products (Third Ed.). The Williams & Wilkins Co., Baltimore, MD.

CLIN--APPENDIX A**CLINICAL****I. Introduction:**

This section of the guidance is designed to assist manufacturers in developing clinical performance data necessary to demonstrate substantial equivalence to a class II lens care product. Whenever possible, CDRH has provided manufacturers with guidance on when to submit clinical performance data and recommended minimum numbers for the size and duration of a clinical study for a new or modified lens care product. When clinical performance data are needed, however, it is the overall responsibility of the manufacturer to design the clinical study with an appropriate number of subjects and sufficient duration to provide adequate data to demonstrate substantial equivalence.

The means for collecting clinical performance data should be designed and conducted in a manner that will provide data constituting valid scientific evidence within the meaning of 21 CFR 860.7. It is not merely a compilation of available subject records. Monitoring of the study, accountability of all subjects, and details of complications or discontinuations are all essential elements.

It is important to note that while CDRH has recommended the appropriate use of controlled studies, such as randomized controlled trials, as a means of minimizing study biases, it also recognizes that some devices with well documented clinical experience may be studied with no control group. This will allow the sponsor to gain experience with the use of the device as well as to confirm safety as predicted from the preclinical data developed for the device.

The recommended preclinical testing is heavily weighted toward demonstrating substantial equivalency to a predicate device. The clinical testing is generally considered as additional confirmatory information to supplement the preclinical data. This is particularly true for "me-too" types of products which are within the marketed concentrations for the active ingredients of the predicate device.

Study protocol suggestions are provided in Clin--Appendix B. It is recommended that the study involve evaluable (completed) subjects divided evenly between independent investigators when applicable. In order to maximize the subjects' exposure to the products during the clinical study, a daily wear schedule should be followed for most products. However, a study of a periodic cleaner, used on weekly intervals, may provide more valuable clinical data concerning efficacy when extended wear subjects are enrolled than a similar study with daily wear subjects.

Clinical study designs may take on a variety of appearances. Concurrent control groups either of equal number to the test group, or utilizing an approximate 2:1 ratio of test to control subject ratio (see table 1) are but two examples. A cross-over study design may also be appropriate in some cases. The use of inpatient controls in a solution study may

not be feasible for some products, but may be utilized if the sponsor desires and determines it to be appropriate.

Historical data may also serve as a control for products with available literature information, or from a manufacturer's previous clinical database, when an adequate justification is provided. If historical controls are used instead of interpatient controls, the historical control group should be defined and adequately characterized for comparison to the test group. When literature information is utilized, a review of applicable published studies along with comparative analysis of the study design, subject populations and outcome measures should be provided. Simply citing references would not be appropriate as a control.

For a clinical study of hydrophilic lenses, the study may be designed with subjects divided as equally as possible between Group I and Group IV lenses. Subjects in clinical studies with RGP lenses should be divided as equally as possible between RGP lens groups requested for 510(k) clearance (currently there are four). If the manufacturer of a lens care solution wishes to recommend its use with a specific type of lens in the labeling, the compatibility with the lens type should be confirmed preclinically and/or during the clinical trial.

Any lens care product study resulting in more than one adverse reaction should include adequate justification in order to establish substantial equivalence to the predicate device in terms of safety and effectiveness. The clinical sample sizes are calculated to be reasonably assured of obtaining at least one complication, as a function of the expected complication rate (5% for a 60 subject group, 10% with a 30 subject group), with a probability of greater than 95%. Therefore, in a subject group of 30 evaluable (completed) subjects exposed to a short term duration of a test product, an adverse event occurrence in 2 to 3 subjects will raise questions as to biocompatibility and fundamental safety of the product.

The clinical protocol for non-significant risk studies requires IRB clearance prior to beginning the study. Applicants should provide the complete protocol along with the study report in their application. FDA recommends the protocol study design, at a minimum, address the following:

1. Statement of the specific study objective(s)
2. Study duration
3. Sample size and selection criteria
4. Number of investigators and selection criteria
5. Methods of reducing study biases (control, etc.)
6. Study materials (lenses and care regimen)
7. Follow-up visit schedule

8. Methods of data collection, monitoring, and analysis

When questions remain concerning the protocol or content and format of a 510(k), sponsors should consult with DOD prior to finalizing their clinical protocol and initiating the investigation.

A "Modified" Trend Analysis Profile (TAP) form should be completed for all clinical studies and included in the clinical report section of the 510(k). The TAP helps identify trends in clinical data which assist the manufacturer and CDRH reviewers in evaluating the substantial equivalence of a device to a legally marketed device. This equivalence is based on whether any differences between the devices would affect safety and effectiveness.

Note that in small clinical studies of short duration (i.e., 30 subjects for 1 month duration), the TAP in addition to a written summary of the clinical trial results may be considered as sufficient documentation for submission. More extensive clinical study submissions should be supported by a TAP as well as a complete clinical report to include the summary reporting tables (Clin--Appendix D).

A sample TAP form is available in Clin--Appendix E. The sample form establishes the basic format that should be presented; however, it should be expanded to include all slit lamp parameters measured as well as visual acuity results and lens replacements. This is especially important when the TAP is provided for the short duration studies without the summary reporting tables. Sponsors with questions concerning the TAP should contact DOD staff for clarification.

Table 1

Example of Distribution of Completed Subjects for Hydrophilic Lens Study with 2:1 Ratio of Test to Control

60-Subject Study

Lens Material	Test Group	Control Group	Total
Group IV	20	10	30
Group I	20	10	30
Subtotal	40	20	60

30-Subject Study

Lens Material	Test Group	Control Group	Total
Group IV	10	5	15
Group I	10	5	15
Subtotal	20	10	30

CLINICAL TESTING MATRIX FOR CLASS II CONTACT LENS CARE PRODUCTS

Product	Same Active Ingredients Within Marketed Concentrations	Same Active Ingredients In Higher Concentrations Than Marketed Products	Same Active Ingredients in Lower Concentrations Than Marketed Products	New Ingredients For Ophthalmic Use or Different Active Ingredient
Saline Solutions				60 subj/1 mo
Daily Cleaner		Footnote A	Footnote B	60 subj/3 mo
Periodic Cleaner		Footnote A	30 subj/1 mo	60 subj/3 mo
Soaking Solution for Disinfection		30 subj/1 mo		60 subj/3 mo
Neutralizer		30 subj/1 mo	Footnote A	60 subj/3 mo
Conditioning Solution		30 subj/1 mo		60 subj/3 mo
In-Eye Solution	30 subj/1 mo	30 subj/1 mo	30 subj/1 mo	60 subj/3 mo

Footnote A: Clinical performance data may need to be submitted depending on the physical/chemical, microbiological and toxicological data collected (i.e., a higher concentration of the active cleaning ingredient in a multi-purpose solution may require submission of clinical data while an increase in concentration of the active ingredient in a periodic cleaner may not unless it is used in conjunction with the disinfection regimen). If necessary, a 30 subject/1 month study should be conducted.

Footnote B: If active ingredient is a surfactant, the sponsor may use either appropriate in vitro tests or conduct a clinical test with 60 subjects/3 months to establish the efficacy of the lower concentration of active ingredient.

In the absence of validated in vitro data, such as non-surfactant cleaning studies, at present a cross-over design with additional in-vitro analysis of worn lenses is an example of one method to demonstrate substantial equivalence to the predicate device. While it may not always be necessary to consult with DOD prior to developing a test protocol, sponsors should note that additional discussion and guidance will be provided if requested.

II. Necessity for Clinical Performance Data and Study Size and Duration Recommendations:

- A. Claim of Substantial Equivalence for a Lens Care Product Based Upon Same Active Ingredients:

1. Claims of substantial equivalence for a lens care product based upon the same active and inactive ingredients within marketed concentrations and the same manufacturing processes will not need clinical performance data provided that the preclinical testing (i.e., physical/chemical, microbiological and toxicological data) supports the claim.

This pertains to an identical "me-too" product for the same product specific intended use and indication as the predicate device. In some cases, the applicant may have obtained referencing rights to predicate device data.

2. Claims of substantial equivalence for a lens care product based upon the same active ingredients within marketed concentrations but different inactive ingredients in some cases require clinical performance data, in addition to physical/chemical, microbiological and toxicological data, to support the claim. This "me-too" product may not be identical to the predicate device since the inactive ingredients in the predicate device may not be identified.

If any of preclinical characteristics differ from the predicate device (data outside the range of the test method) the sponsor should justify why this characteristic difference will not impact upon the safety and effectiveness or supply supporting clinical performance data.

When clinical performance data are necessary, such as for in-eye solutions, it is recommended that this study involve at least thirty (30) evaluable subjects followed for at least 1 month.

3. Claim of substantial equivalence based upon same active ingredients in higher or lower concentrations than marketed products generally require clinical performance data to be submitted depending on the physical/chemical, microbiological and toxicological data collected to support the claim.

When clinical performance data are necessary it is recommended that this study involve at least 30 evaluable subjects followed for at least 1 month.

- B. Claim of Substantial Equivalence for a Lens Care Product with New Ingredients for Ophthalmic Use or Different Active Ingredient:

Claims of substantial equivalence for a lens care product with new ingredients for ophthalmic use or different active ingredient require submission of clinical performance data, in addition to physical/chemical, microbiological and toxicological data, to support the claims. It is recommended that this clinical study involve at least sixty (60) evaluable (completed) subjects followed for at least 3 months.

C. Labeling Claims with Additional Indications:

The sponsor should design the study to collect data demonstrating the substantial equivalence of the lens care product to a legally marketed device in terms of the safety and effectiveness of the device. Additional indications could include use of the product with a different lens material [e.g., rigid gas permeable lenses (hydrophobic) when previously indicated for soft hydrophilic lenses, or an additional product specific intended use such as saline solution repackaged and relabeled as a rewetting drop].

Applicants should select an appropriate predicate device for comparisons and determination of substantial equivalence. The appropriate clinical testing matrix for the additional claim(s) should be referred to for guidance. Applicants may also contact DOD prior to initiating studies if they have questions.

III. Study Summary

For the purpose of ease in the submission of clinical performance data in support of a claim of substantial equivalence, DOD recommends that the following outline be utilized:

A. Introduction

1. Purpose
2. Statement of compliance
3. List of investigators to include number of eyes enrolled by each; control and trial, completed and discontinued

B. Materials and Methods

1. Study materials; to include lens(es) utilized and any solutions in addition to the study solution for both test and control subjects
2. Study design and procedures; to include randomization procedures, if utilized
3. Data analysis

C. Subjects

1. Demographic data
2. Completed and discontinued for both control and trial groups

D. Data to support substantial equivalence - sample tables included in Clin--Appendix D (data for control eyes should be reported separately from data for the trial eyes)

1. Adverse Reactions
2. Slit Lamp Examination
3. Symptoms/Problems/Complaints
4. Visual Acuity
5. Average Wear Time
6. Discontinued Eyes
7. Lens Replacements

Note: *Keratometric changes and refractive changes have been deleted as any event severe enough to cause these types of changes in experienced lens wearers would manifest itself in other categories*

E. "Modified" Trend Analysis Profile - Clin--Appendix E

F. Conclusion

CLIN--APPENDIX B

CLINICAL PROTOCOL SUGGESTIONS

OUTLINE

- I. ALL STUDY DESIGNS
- II. LENS CARE PRODUCT STUDIES
 - A. PROTOCOL CONSIDERATIONS
 - 1. Statement of Specific Study Objective(s)
 - 2. Sample Size and Study Duration
 - 3. Sample Selection Criteria (a-e)
 - 4. Investigator Selection Criteria
 - 5. Methods of Study Control
 - 6. Adjunct Solutions
 - 7. Visit Schedule
 - a. General Information
 - b. Follow-up Schedules
 - 8. Monitoring and Accountability
 - a. Enrollment/Accountability
 - b. Visit Forms
 - c. Monitoring Responsibilities
 - d. Methods of Analysis
 - B. METHODS OF DATA COLLECTION AND ANALYSIS
 - 1. Adverse Reaction Data
 - 2. Slit Lamp Findings
 - 3. Symptoms/Problems/Complaints
 - 4. Visual Acuity
 - 5. Average Wear Time
 - 6. Discontinuation
 - 7. Lens Replacements
- III. PROBLEMS/QUESTIONS

I. ALL STUDY DESIGNS:

It is important that the means for collecting clinical performance data be designed and conducted in a manner that will provide data constituting valid scientific evidence within the meaning of 21 CFR 860.7. In that section, the essentials of a well-controlled clinical investigation are discussed. During the design of a study the impact of the protocol on final product labeling should be kept in mind.

II. LENS CARE PRODUCT STUDIES:

A. Protocol Considerations:

The clinical protocol should, at a minimum, address the following:

1. Statement of the Specific Study Objective(s)
2. Sample Size (interpatient controls) and Study Duration-- is dependent upon the basis for the claim of substantial equivalence and formulation.
 - a. At least 60 evaluable subjects (one evaluable subject is defined as two completed eyes) for a minimum of 3 months for a claim of substantial equivalence based upon the same intended use, but composed of new ingredients for ophthalmic use or different active ingredient.
 - b. At least 30 evaluable subjects for a minimum of 1 month for a claim of substantial equivalence based upon the same intended use, composed of the same active ingredients as the predicate product, a "me-too" product (refer to matrix).
3. Sample Selection Criteria

The following definitions should be used when reading this section.

Normal: a set of clinical findings which would not prevent a subject from contact lens wear. For example, a small corneal scar located off the visual axis which is long-standing may not preclude the use of cosmetic contact lenses.

Abnormal: a finding which would preclude a subject from consideration as an acceptable lens candidate.

- a. Subjects should have worn contact lenses successfully previously (so as to not add another variable to the study).

- b. Subject selection for entry into the study should meet the entry criteria established in the protocol.
- c. In appropriately randomized, controlled studies, the subjects should be randomly assigned to either the control or the test group and the sponsor should detail the randomization procedure.
- d. Subjects should have normal eyes and use no ocular medications. A normal eye is defined as having the following characteristics:
 - (1) no anterior segment infection, inflammation or abnormality;
 - (2) no other active ocular or systemic disease that would contraindicate contact lens wear; and
 - (3) no medications that would contraindicate contact lens wear.
- e. Subjects with normal eyes not correctable to 20/40 with spectacles may be enrolled, but should be analyzed separately.

A minor positive finding should not disqualify a subject from participating in a clinical study if the investigator determines that the finding does not interfere with contact lens wear or cause the eye to become compromised from contact lens wear. The investigator should use clinical judgment to determine a subject's eligibility based on any trace pre-fitting observations and the study protocol as designed by the monitor and sponsor.

4. Investigator Selection Criteria

The sponsor should select an appropriate number of investigators to minimize biases. The training, experience, and objectivity of investigators should also be considered when attempting to reduce study biases.

As an example, a ratio of evenly assigning enough subjects to each investigator to allow for an evaluation of trends between investigators would be two (2) or three (3) investigators for a 30 subject study, and three (3) or four (4) investigators in a 60 subject study. The targeted minimum number of subjects per site would then be 10 to 15 in a small study, and 15 to 20 in the large study. These numbers also allow for the poolability of data for analysis.

5. Methods of Study Control

The sponsor should address those features of the study design which have been devised to minimize biases. CDRH suggests protocols which incorporate the appropriate use of controlled studies as a means of minimizing biases in clinical data. Randomized controlled clinical trials (RCT) may be appropriate in some cases, but not in all cases, refer to the Introduction section of Clinical (Clin--Appendix A). If the sponsor chooses to use historical controls instead of interpatient controls, the historical control group should be defined and adequately characterized for comparison to the test group.

For further information refer to texts such as:

Friedman, L.M. et al. Fundamentals of Clinical Trials. John Wright-PSG Inc., Boston, MA, 1982.

Meinert, C.L. and S. Tonascia. Clinical Trials - Design, Conduct and Analysis. Oxford University Press, New York, NY 1986.

6. Adjunct Solutions

All lens care products used in the study should be specified. The surface quality of the lenses should also be assessed for such findings as deposits, cracking or crazing. CDRH recommends the use of grading systems to standardize such findings. One example of a grading system for deposits is the modified Rudko Method which is discussed in an article by R.A. Hathaway and G.E. Lowther in the Journal of the American Optometric Association, 49 (3) 259-266, 1978.

Another grading scale is as follows:

Lens Surface Characteristics

Front Surface Wettability:

- 0 = a smooth uniformly reflecting surface
- 1 = a coarse hazy surface which seems resolved momentarily with each blink and becomes exacerbated with staring
- 2 = a stable dry (non-wetting) area of some magnitude
- 3 = gross crystalline or amorphous deposits

Front Surface Deposits:

- 0 = absent, clean surface
- 1 = very slight, only visible after tear film drying
- 2 = slight, visible deposits easily removed
- 3 = moderate, deposits adherent and not removable
- 4 = severe, non-removable deposits and comfort affected

Findings of an increase in the frequency of use for lubricants, in-office cleanings, or need for enzyme use should be evaluated and addressed by the applicant.

7. Visit Schedule

a. General Information

All subjects in a study should be on the same follow-up schedule. In the event an ocular abnormality is observed at any visit, the investigator should see the subject as frequently thereafter as necessary to treat and eliminate the abnormality. (Documentation of abnormalities will be discussed later.) The reason for each unscheduled visit should be reported in the 510(k).

b. Follow-up Schedules (after the initial dispensing of new lenses and lens care products)

The following schedule contains target dates, rather than absolute dates for follow-up. In most cases, the sponsor may assign acceptable windows around each target date to further clarify the visit schedule for the investigator:

One Month Study: 1 week, 2 weeks, 4 weeks.

Three Month Study: 1 week, 4 week, then monthly through study.

Any subject reporting for an unscheduled visit should be documented on the reporting tables under "Unscheduled Visit."

8. Monitoring and Accountability

(Reference 21 CFR 812 Subparts C and E)

a. Enrollment/Accountability

A subject should be considered enrolled when he or she signs the informed consent form. This form should be signed prior to dispensing of any lens care products. All subjects enrolled should be accounted for even if they are not dispensed lens care products. Once enrolled, a subject is considered "active" and should be accounted for at every visit until completion of, or discontinuation from, the study.

b. Visit Forms

A visit form should be filled out and signed by the investigator performing the examination at the time of the scheduled or unscheduled visit. Adverse reaction reports must be completed in accordance with 21 CFR 812.46(b) and submitted to CDRH.

c. Monitoring Responsibilities

If an investigator is not complying with the signed agreement, the investigational plan or other conditions imposed by the IRB or CDRH, the sponsor should either secure compliance or discontinue shipments of the device to the investigator and end his or her participation in the study.

d. Methods of Analysis

The sponsor should summarize the methods of analysis including any appropriate statistical methods of evaluating the data.

B. Methods of Data Collection and Analysis:

This section discusses the data which are provided to support the claim of substantial equivalence. The Summary Reporting Tables (Clin-Appendix D) may be used by sponsors as a basis for developing clinical reporting forms.

1. Adverse Reaction Data

CDRH believes an "adverse reaction" would include, but not be limited to a hazardous, sight-threatening condition such as: corneal ulcers, severe corneal abrasion > 2 mm in diameter, iritis, other ocular infections or inflammations, corneal scarring, or permanent loss of vision.

Photodocumentation or detailed drawings that detail the size, location and depth of the adverse reaction should be provided. Infections should be cultured.

The sponsor should detail the events of all adverse reactions including all treatment(s) and diagnoses through the resolution of the event.

Events which are not sight-threatening should be graded and reported as significant findings in the appropriate category such as slit lamp findings or the symptoms/problems/complaint section.

Non-sight-threatening events may include, but are not limited to, the following: giant papillary conjunctivitis, epiphora, dry eyes, and irritation.

2. Slit Lamp Findings

Slit lamp examinations should be performed at each visit. The investigator should record all positive and negative (grade 0) findings, not only those which are considered to be clinically significant. The results should be tabulated, and all findings over grade 2 should be explained in the 510(k).

An example of a SLIT LAMP FINDINGS CLASSIFICATION SCALE is included in Clin--Appendix C. Other suitable well defined classification scales can be found in the FDA PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR DAILY WEAR CONTACT LENSES or the ISO standard, Optics and Optical Instruments - Contact Lens and Contact Lens Care Products - Guidelines for Clinical Investigations, ISO/DIS 11980.

3. Symptoms/Problems/Complaints

Subjective data should be collected at each visit and tabulated in the 510(k). These data are used in conjunction with objective findings in the assessment of safety and effectiveness.

Additionally, the following information may be submitted:

Subjective Acceptance

Below are samples of acceptable grading scales for a limited number of parameters. Please refer to Table 5 of Clin--Appendix D, Informative Summary Reporting Tables, for additional sample parameters.

Other suitable well defined scales, such as that found in the ISO standard, Optics and Optical Instruments - Contact Lens and Contact Lens Care Products - Guidelines for Clinical Investigations, ISO/DIS 11980, may also be used. Sponsors may also consider utilizing an alternative to the numeric rating scale, such as a visual analog scale, provided the method is appropriate for collection and analysis of the data.

Comfort:

- 0 = Excellent, cannot be felt
- 1 = Very comfortable, just felt occasionally
- 2 = Comfortable, noticeable but not irritating
- 3 = Slightly uncomfortable, just irritating or annoying
- 4 = Very uncomfortable, very irritating or annoying
- 5 = Causes pain, lens cannot be tolerated

Vision:

- 0 = Excellent, cannot notice any visual loss
- 1 = Very good, just noticeable and very occasional reduction
- 2 = Good, occasional noticeable but acceptable reduction
- 3 = Poor, noticeable but acceptable reduction
- 4 = Very poor, marked and unacceptable reduction
- 5 = Unacceptable, lens cannot be worn

Handling:

- 0 = excellent, no problems with lens insertion and removal
- 1 = Very good, occasional difficulty with lens insertion and removal
- 2 = Good, some problems but insertion and removal usually successful
- 3 = Poor, difficult and very occasional unsuccessful insertion/removal
- 4 = Very poor, difficult and occasional unsuccessful insertion/removal
- 5 = Unmanageable, lenses impossible to handle

4. Visual Acuity (VA) Data

Distance VA should be taken at each visit. Although other acceptable scales such as Snellen Acuity are available, the use of logMAR progression VA charts with equal steps between successive lines is recommended.

For purposes of submission, the initial VA (best corrected with the contact lens) should be compared to the VA results with the contact lens at the final visit.

VA decreases of 2 or more lines should be reported with explanations. Investigator comments and explanations for all decreases of 2 or more lines at final visit compared to initial visit should be included. Additionally, a similar decrease in VA during the course of the study should be reported and explained.

5. Average Wear Time (AWT)

The lens AWT should be recorded at each visit. A tabulated report of AWT in hours, or days as appropriate, by visit should be provided to assess trends during the

study. When data are collected for both daily lens wearers and extended lens wearers, these data should be analyzed separately.

6. Discontinuations

Complete data should be provided on all discontinued subjects including the reason for discontinuation and visual status at the final visit. If problems persist, the subject should be followed until resolution of the problem. All data which would normally be collected at the final study visit should also be collected at the discontinued subject's last visit. Copies of subject report forms for all discontinued subjects should be provided in the submission.

7. Lens Replacements

The reason for each replacement should be tabulated in a manner which allows for trend analysis during the course of the study. Lens replacements for the following reasons should be further explained: discoloration, response to physiological problems, slit lamp findings, or "other."

III. PROBLEMS/QUESTIONS:

When questions remain concerning the protocol or content and format of a 510(k), sponsors should consult with DOD prior to finalizing their clinical protocol and initiating the investigation.

CLIN--APPENDIX C

SLIT LAMP FINDINGS CLASSIFICATION SCALE

A. EDEMA

Corneal edema should be classified according to the haziness of the epithelium, the number of microcysts observed, and the clouding of the stroma.

EPITHELIAL EDEMA

- 0 - NONE: None: No epithelial or sub-epithelial haziness. Normal transparency
- 1 - TRACE: Barely discernible localized epithelial or subepithelial haziness
- 2 - MILD: Faint but definite localized or generalized haziness
- 3 - MODERATE: Significant localized or generalized haziness
- 4 - SEVERE: Definite widespread, epithelial cloudiness giving dull glass appearance to cornea, or numerous coalescent bullae (Note the number and location of bullae)

EPITHELIAL MICROCYSTS

- 0 - NONE: No microcysts
- 1 - TRACE: 1 to 20 microcysts
- 2 - MILD: 21 to 50 microcysts
- 3 - MODERATE: 51 to 100 microcysts
- 4 - SEVERE: > 100 microcysts or bullae

The presence/absence of vacuole or bullae should be documented along with their numbers. The presence of bullae should be considered as reportable grade 4 severe epithelial edema.

STROMAL EDEMA

- 0 - NONE: None: No stromal cloudiness. Normal transparency
- 1 - TRACE: Barely discernible localized stromal cloudiness
- 2 - MILD: Faint but definite localized or generalized stromal cloudiness
- 3 - MODERATE: Significant localized or generalized stromal cloudiness
- 4 - SEVERE: Definite widespread, stromal cloudiness, or numerous striae. (Note the number and location of striae)

B. CORNEAL NEOVASCULARIZATION

Maximal corneal vascularization should be reported according to the following scale:

- 0 - NONE: No vessel penetration
- 1 - TRACE: < 1.0 mm vessel penetration
- 2 - MILD: 1.0 mm - 1.5 mm vessel penetration
- 3 - MODERATE: 1.5 mm - 2.0 mm vessel penetration
- 4 - SEVERE: Vessel penetration > 2.0 mm.

Optionally the depth and location of vessel penetration can also be reported as follows:

Depth

- a. superficial
- b. stromal

Location

N	Nasal	T	Temporal
I	Inferior	S	Superior
C	Circumferential	X	Other (describe)

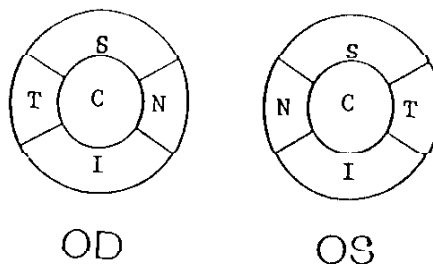
C. CORNEAL STAINING

It is recommended that sponsors design data collection forms to obtain information concerning the location of corneal staining so that peripheral staining can be differentiated from central staining.

Maximal corneal staining should be recorded according to the following scale:

- 0 - NONE: No staining
- 1 - TRACE: Minimal superficial staining or stippling
 - a. Dimpling, discrete dot staining, OR
 - b. Trace superficial lens insertion marks or foreign body tracks
- 2 - MILD: Regional or diffuse punctate staining
 - a. Central or generalized, OR
 - b. Peripheral including 3-9 o'clock staining, OR
 - c. Mild abrasion or foreign body tracks
- 3 - MODERATE: Dense coalesced staining up to 2 mm diameter
 - a. Corneal abrasion
 - b. Foreign body track
- 4 - SEVERE: Dense coalescent staining greater than 2 mm in diameter or full thickness abrasion.

Location: N - Nasal, T - Temporal, I - Inferior, S - Superior,
C - Central



D. BULBAR HYPEREMIA

Maximal limbal and bulbar hyperemia should each be recorded on a 5 point scale as follows:

- 0 - NONE: No hyperemia present
- 1 - TRACE: Slight regional hyperemia
- 2 - MILD: Diffuse hyperemia
- 3 - MODERATE: Marked regional or diffuse hyperemia
- 4 - SEVERE: Diffuse episcleral or scleral hyperemia

E. PALPEBRAL CONJUNCTIVAL OBSERVATIONS

The location of maximal conjunctival response should be documented according to the following scale:

- 0 - NONE: Uniform satin appearance of conjunctiva
- 1 - TRACE: Slight conjunctival injection without texture
- 2 - MILD: Mild or scattered papillae/follicles less than 1 mm in diameter
- 3 - MODERATE:
 - a. Significant papillae/follicles less than 1 mm in diameter, and/or marked conjunctival injection
 - b. Staining of the top of one papilla
- 4 - SEVERE:
 - a. Localized or generalized papillae/follicles 1 mm or more in diameter
 - b. Staining of the top of more than 1 papilla

Optionally, the conjunctival response can also be recorded for each of the four lid areas:

Upper lid

- 1 - Superior tarsal conjunctiva
- 2 - Middle tarsal conjunctiva
- 3 - Inferior (lid margin region) tarsal conjunctiva

Lower lid

- 4 - Palpebral conjunctiva of lower lid

F. OTHER COMPLICATIONS (List all reports by specific finding and grade by severity)

This section is intended to capture less commonly observed clinical entities such as corneal infiltrates, conjunctival infection, EKC, corneal ulcers, iritis, lens adhesions and recurrent erosion. The complication should be identified and described according to the following generic scale.

Example provided for infiltrates, but the concept is applicable to all findings:

- 0 - NONE: No other significant biomicroscopic findings
- 1 - TRACE: Minimal finding such as one faint peripheral infiltrate which does not stain
- 2 - MILD: Mild findings such as a few faint infiltrates
- 3 - MODERATE: Significant findings such as multiple, dense infiltrates
- 4 - SEVERE: Severe finding such as marked infiltrates with overlying staining

CLIN--APPENDIX D

INFORMATIVE SUMMARY REPORTING TABLES
(Provided for reference)Table 1 Notes:

TITLE: Accountability of Eyes Enrolled and Distribution by Status

PURPOSE: To ensure a complete accounting of all eyes enrolled in the investigation.

General: Six status subgroups are identified and defined below. In all cases status is as of the cutoff date of the study at which time data were tabulated for submission.

Enrolled Dispensed: All subjects who signed an informed consent form prior to having lens care product(s) dispensed to them.

Completed Eyes: Eyes which used the lens care product(s) for the prescribed investigational period and for which a final visit form was completed and submitted.

Active Eyes: Eyes which were using the lens care product(s) but had not completed the prescribed investigational period.

Discontinued Eyes: Eyes which had ceased using the lens care product(s) prior to completion of the prescribed investigational period.

Incomplete Eyes: Eyes which have completed the prescribed investigation period but for which a final visit report has not been received by the sponsor.

Enrolled But Not Dispensed: Eyes considered enrolled because the subject had signed an informed consent form, but for which lens care product(s) had not been dispensed.

TABLE 1
ACCOUNTABILITY BY EYES ENROLLED IN THE STUDY
AND DISTRIBUTION BY STATUS

Status	Number of Eyes
<u>Enrolled Dispensed</u>	
<u>Completed</u>	C/T
<u>Active</u> (Visit Completed)	
Dispensing	C/T
1st follow up	C/T
2nd follow up	C/T
(list through) nth follow up	<u>C/T</u>
Total Active	C/T
Discontinued	C/T
Incomplete	<u>C/T</u>
Total Dispensed	C/T
<u>Enrolled Not Dispensed</u>	<u>C/T</u>
<u>Total Enrolled</u>	C/T

C = # control eyes

T = # trial eyes

Table 2 Notes:

TITLE: Demographics

PURPOSE: To provide demographic data.

TABLE 2
DEMOGRAPHICS

Age of Subjects: From _____ To _____, Average _____.

Sex: Female _____, Male _____, Ratio _____.

Table 3 Notes:

TITLE: Adverse Reactions (3A), SLFs Requiring Treatment (3B), SPCs Requiring Treatment (3C)

PURPOSE: To provide a detailed accounting of any condition occurring in any eye in the study requiring treatment to ensure ocular health.

DEFINITIONS:

Adverse Reaction: Considered to include, but not be limited to a hazardous, sight-threatening condition such as: corneal ulcers, iritis, other ocular infections or inflammations, corneal scarring, or permanent loss of vision.

SLFs Requiring Treatment: Any slit lamp finding in any examination, scheduled or unscheduled, that requires treatment, including temporary discontinuation of lens wear, to maintain normal ocular health. This does not include SLFs that are corrected by refitting of lenses without discontinuation of wear or by retraining subjects in proper lens care.

SPCs Requiring Treatment: Any symptom, problem or complaint that requires treatment, including temporary discontinuation of lens wear, to maintain normal ocular health. This does not include SPCs that are corrected by refitting of lenses without discontinuation of wear or by retraining of subjects in proper lens care.

GENERAL: Outcome should include cause of condition, treatment required, resolution including VA, damage to the eye if any, and whether or not discontinued from the study.

TABLE 3
ADVERSE REACTIONS (3A)

ADVERSE REACTION	TIME IN INVESTIGATION	OUTCOME
1.		
2.		
3.		
4.		
etc.		
Total eyes with adverse reactions_____.		

SLFs Requiring Treatment (3B)

SLF	TIME IN INVESTIGATION	OUTCOME
1.		
2.		
3.		
4.		
etc.		
Total eyes with SLFs requiring treatment _____.		

SPCs Requiring Treatment (3C)

SPC	TIME IN INVESTIGATION	OUTCOME
1.		
2.		
3.		
4.		
etc.		
Total eyes with SPCs requiring treatment_____.		

Table 4 Notes:

TITLE: Slit Lamp Findings By Visit, Tabulated By Eyes and Incidence Rate

PURPOSE: To provide comprehensive tabulation of SLF data by visit (time in study) and completeness of recording.

GENERAL:

Separate tables should be prepared and clearly identified for:

Completed Control Eyes (Table 4A)
 Completed Trial Eyes (Table 4B)
 Discontinued Control Eyes (Table 4C)
 Discontinued Trial Eyes (Table 4D)

In Tables 4A and 4B, total eyes should be the same for all visits and the same as the number of eyes completed in Table 1.

In Tables 4C and 4D, total eyes will vary by visit as a function of when subjects discontinued.

Intermediate visits should be numbered in sequence and the time in study for each sequence number should be provided in a footnote to Table 4A.

Tables 4 (A, B, C & D) should be expanded laterally as necessary to provide a data column for each intermediate visit.

For each SLF (e.g., edema, vascularization, etc.) a horizontal row should be provided for each SLF grade up through the highest grade recorded for each SLF.

Slit Lamp Findings reported between scheduled visits should be reported under "Unscheduled Visits."

Percentages should be calculated in accordance with the following formula:

= Eyes at grade of SLF or eyes not recorded

% = Incidence rate or percent eyes not recorded

% Incidence Rate = $\frac{\text{Eyes at grade of SLF}}{\text{Total Eyes at visit}} \times 100$

% Eyes not recorded = $\frac{\text{Eyes not recorded}}{\text{Total eyes at visit}} \times 100$

Any SLFs that require treatment should be listed in Table 3B.

In the "Eyes Not Recorded" row, list the number of eyes and percent not recorded for each visit.

Table 5 Notes:

TITLE: Symptoms, Problems, and Complaints by Visit, Tabulated by Eyes and Incidence Rates

PURPOSE: To provide comprehensive tabulation of data on SPC by visit (time in study).

GENERAL:

Separate tables should be prepared and clearly identified for:

- Completed Control Eyes (Table 5A)
- Completed Trial Eyes (Table 5B)
- Discontinued Control Eyes (Table 5C)
- Discontinued Trial Eyes (Table 5D)

In Tables 5A and 5B, total eyes should be the same for all visits and the same as the number of "eyes completed" in Table 1.

In Tables 5C and 5D, total eyes will vary by visit as a function of when subjects discontinued.

Intermediate visits should be numbered in sequence and the time in study for each sequence number should be provided in a footnote to Table 5A.

Tables 5 (A, B, C & D) should be expanded laterally as necessary to provide a data column for each intermediate visit.

SPCs reported between scheduled visits should be reported under "Unscheduled Visits."

Percentages should be calculated in accordance with the following formula:

= Eyes reporting that SPC

% = Incidence rate at visit

$$\% \text{ Incidence Rate} = \frac{\text{Eyes reporting SPC at final visit}}{\text{Total eyes at final visit}} \times 100$$

Any SPCs that require treatment should be listed in Table 3C.

TABLE 5
SYMPTOMS, PROBLEMS, AND COMPLAINTS BY VISIT
TABULATED BY EYES AND INCIDENCE RATES

Initial Dispensing Visit	Intermediate Visits						Total
	1	2	3	4	Unscheduled		
Total Eyes At Visit	XX	XX	XX	XX	XX	XX	XX
	# %	# %	# %	# %	# %	# %	# %
None	X	X	X	X	X	X	XX
(The following are examples of parameters assessed. Some may not be applicable for a given study design)							
Discomfort							
Excess Tearing							
Photophobia							
Halos							
Itching							
Burning							
Spectacle Blur							
Variable Vision							
Blurred Vision							
Lens Needs Cleaning							
Lens Awareness							
Other (Specify)							
Total Positive Reports	X	X	X	X	X	X	XX

Table 6 Notes:

TITLE: Visual Acuity (VA) Results with Contact Lens at Final Visit

PURPOSE: To provide VA data for the contact lens in a concise format.

GENERAL:

Separate tables should be prepared and clearly identified for:

- Completed Control Eyes (Table 6A)
- Completed Trial Eyes (Table 6B)
- Discontinued Control Eyes (Table 6C)
- Discontinued Trial Eyes (Table 6D)

In addition to the data on the table for the final visit, the data in the "Visual Acuity Summary" should be provided. The number of eyes that had a VA of 2 or more lines on the logMAR progression scale worse than the initial best corrected VA should be provided for each visit, and an explanation should be provided for each instance in the second section of Table 6.

Number and percentage in each horizontal row of each VA column refer to the number of eyes in the best corrected column for the corresponding row. Percentage should be calculated in accordance with the formula on the table.

TABLE 6
VISUAL ACUITY RESULTS WITH CONTACT LENS
AT FINAL VISIT (EXAMPLE PROVIDED IN logMAR NOTATION)

Initial Best Corrected	Number of Eyes	-0.1 # %	0.0 # %	0.1 # %	0.2 # %	0.3 . . . # %	Not Reported # %	Totals # %
-0.1	X X	X X						X X
0.0	X X	X X						X X
0.1	X X	X X						X X
0.2	X X	X X						X X
0.3	X X	X X						X X
(Continue as Needed)	X X	X X						X X
Totals	X X	X X						X X

$$\% \text{ at each VA} = \frac{\# \text{ of eyes at each VA (or total)}}{\# \text{ of eyes at initial best (or total) corrected of corresponding row}} \times 100$$

Visual Acuity Summary:

eyes with initial best corrected VA of 0.2 logMAR or better ____.

eyes with final VA with lens of 0.2 logMAR or better ____.

eyes with final VA with lens within +/- 1 logMAR progression of best corrected ____.

eyes with final VA with lens of worse than +/- 1 logMAR progression of best corrected ____.

TABLE 6 (cont.)
LISTING OF EYES THAT CHANGED 2 OR MORE LINES ON THE
VISUAL ACUITY SCALE

Investigator	Subject	Eye	Initial VA	VA at Visit	Reason
<hr/>					
1.					
2.					
3.					
etc.					

Table 7 Notes:

TITLE: Average Wear Time per Visit

PURPOSE: To provide an accounting of wearing time by time in study.

GENERAL:

Separate tables should be prepared and clearly identified for:

Completed Control Eyes (Table 7A)

Completed Trial Eyes (Table 7B)

Discontinued Control Eyes (Table 7C)

Discontinued Trial Eyes (Table 7D)

Number and percentage refer to the number of eyes in the average wearing time column for the corresponding row. Percentage should be calculated in accordance with the following formula:

$$\% \text{ at each time} = \frac{\# \text{ of eyes at each time}}{\# \text{ of total eyes}} \times 100$$

TABLE 7
AVERAGE WEAR TIME

Wearing time	Intermediate Visits				Final Unscheduled	Visit
	1	2	3	4		
	# %	# %	# %	# %	# %	# %
0 to 6.0	X X	X X	X X			
6.1 to 12.0						
12.1 to 18.0						
1 overnight						
2 overnights						
3 overnights						
4 overnights						
5 overnights						
6 overnights						
Not reported						
<hr/>						
Wearing time average/visit						

Table 8 Notes:

TITLE: Discontinued Eyes Tabulated by Completed Visits and Reasons for Discontinued with Incidence Rates

PURPOSE: To provide comprehensive data on all discontinued eyes with reasons for discontinuation, time in study, and incidence rates.

GENERAL:

Eyes known to have discontinued between scheduled visits should be listed in the "Unscheduled Visits" column.

Total discontinuations should be provided for each intermediate visit. Aggregate discontinuations and aggregate incidence rate should be calculated for each reason and for total discontinuations.

Aggregate incidence rates should be calculated in accordance with the formula shown on the table. It is recognized that this formula will result in some error because active and incomplete eyes are not taken into account. However, this error will be small unless the discontinuation rate, number of active eyes, or number of incomplete eyes is excessive. In such cases, submission of additional data and subsequent review may be required.

Note: More than one reason may be given for discontinuation. In such a case, note only the principal reason on the table and identify the additional reasons in a footnote to the table.

TABLE 8
DISCONTINUED EYES TABULATED BY COMPLETED VISITS
AND REASONS FOR DISCONTINUED WITH INCIDENCE RATES

Reasons for Discontinuation	Eyes at (or after) Visit Completed					Unsch.	Aggre. Disc.	%
	INITIAL	1	2	3	4			
Visual acuity								
Positive SLF								
Adverse Reaction								
Lens Positioning								
Discomfort								
Handling Problem								
Disinterest								
Lost-to-Follow-up								
None Given								
Other (Specify)								
Total								

$$\% \text{ Incidence} = \frac{\text{Aggregate eyes discontinued per reason}}{\text{Total eyes completed} + \text{total eyes disc.}} \times 100$$

C = # control eyes
T = # trial eyes

Table 9 Notes:

TITLE: Lens Replacements by Visit

PURPOSE: To provide a tabulation of all lenses replaced during the study by reason for replacement.

GENERAL:

Separate tables should be prepared and clearly identified for:

Completed Subjects (Table 9A)

Discontinued Subjects (Table 9B)

Lenses replaced for visual acuity, pathology or other physiological reasons must be listed individually, with the specific reason for replacement and the visual acuity with the replacement lens.

Number and percentage refer to the number of eyes for each reason for replacement for the corresponding row. Percentage should be calculated in accordance with the following formula:

$$\% \text{ of eyes with lenses replaced} = \frac{\# \text{ of eyes at each visit}}{\# \text{ of total eyes} \times 100}$$

TABLE 9
LENS REPLACEMENTS BY VISIT

Reason for Replacement	INITIAL Total	Intermediate Visit								Unsched.		
		1		2		3		4				
		#	%	#	%	#	%	#	%			
	#	%	#	%	#	%	#	%	#	%	#	%
Visual Acuity	C/T			C/T	C/T	C/T	C/T	C/T	C/T			C/T
Comfort												
Pathology												
Base Curve												
Diameter												
Lost												
Torn												
Lens Deposits												
Bad Edge												
Bad Surface												
Discoloration												
Other (Specify)												
Totals	C/T			C/T	C/T	C/T	C/T	C/T	C/T			C/T

C = # control eyes

T = # trial eyes

CLIN--APPENDIX E**"MODIFIED" TREND ANALYSIS PROFILE**

The "Modified" Trend Analysis Profile (TAP) is intended to assist in the identification of trends. The TAP provides the number of events (e.g., adverse reactions), that occur at each visit of the study as well as the total number of events occurring during the study. In a sense, it is similar to a life table analysis in that it may quickly indicate the interval of time from the entry of subjects into the trial until the occurrence of specific events (e.g., adverse reactions). It may also reveal data trends that would be difficult to glean from the clinical report; however, it is not intended to replace the clinical report or a 510(k) Summary of Safety and Effectiveness.

The following directions outline the appropriate methods recommended for completing the TAP form. CDRH anticipates that the TAP form may evolve over time as CDRH and sponsors discover improved means of presenting trend data.

Item	Category	Instructions for completing TAP
1	Time in Study	This entry identifies how far the study has progressed (e.g., 1 week or 1 month into the study). (The data reported in a given column should represent only the data collected during that particular time interval. Only data in the Total column, at the far right of the table, are cumulative for the entire study.)
2	Total # of Eyes	This number includes the total number of eyes, either active or discontinued, that were examined during that time interval.
3	D/C Eyes	This number includes all the eyes discontinued during that time interval.
4	Average Wear Time	This number is the average wear time reported by all eyes, either active or discontinued, during that time interval.
5	Lens Replacements	This number is the actual number of lenses replaced during that time interval.
6	All Adverse Reactions	Each adverse reaction should be recorded only at the onset of the event. Follow-up visits for that particular event should not be recorded here.
7	All Corneal Ulcers	This is a subset of the Adverse Reactions discussed in Item 5. For this entry, each ulcer should be recorded only at the onset in the same manner that adverse reactions were reported in Item 5.

- 8 All Iritis This is a subset of the Adverse Reactions discussed in Item 5. For this entry, each iritis episode should be recorded only at the onset in the same manner that adverse reactions were reported in Item 5.
- 9 Total Reports Staining This number includes all staining reports which occurred during that time interval. If there are multiple reports for one eye, each report should be counted in this category.
- 10 Staining Reports >Gr 2 This number includes all staining reports greater than grade 2, which occurred during that time interval. If there are multiple reports > grade 2 for one eye, each report should be counted in this category.
- 11 Total # of Eyes Reporting Staining: This number includes the number of eyes that had staining reports one or more times during the study. Even if there are multiple reports for one eye, only one report should be counted.
- 12-14 Edema Categories The instructions for completing the edema entries correspond exactly to the instructions for completing the staining categories (Items 8-10 above). Follow the instructions for Items 8-10 substituting the word "edema" for the word "staining."
- 15-17 Injection Categories The instructions for completing the injection entries correspond exactly to the instructions for completing the staining categories (Items 8-10 above). Follow the instructions for Items 8-10 substituting the word "injection" for the word "staining."
- 18-20 Neovasc. Categories The instructions for completing the neovascularization entries correspond exactly to the instructions for completing the staining categories (Items 8-10 above). Follow the instructions for Items 8-10 substituting "neovascularization" for the word "staining."
- 21 Total Visits This includes the total number of visits occurring during this time interval.
- 22 Total Missed Visits This includes the total number of missed visits during this time interval.

CLIN--APPENDIX E

"MODIFIED" TREND ANALYSIS PROFILE (TAP)

SPONSOR/510(K) No. _____

TRADE NAME: _____

No. Eyes Enrolled: _____

Generic Indication _____

	VISIT NUMBER						
	1	2	3	4	5	6	TOTALS
TIME IN STUDY							
TOTAL # OF EYES							
D/C EYES							
AVERAGE WEAR TIME							
LENS REPLACEMENTS							
ALL ADVERSE REACTIONS							
ALL CORNEAL ULCERS							
ALL IRITIS							
TOTAL REPORTS STAINING							
STAINING REPORTS > GR 2							
TOTAL NUMBER OF EYES REPORTING STAINING							
TOTAL REPORTS EDEMA							
EDEMA REPORTS > GR 2							
TOTAL NUMBER OF EYES REPORTING EDEMA							
TOTAL REPORTS INJECTION							
INJECTION REPORTS > GR 2							
TOTAL NUMBER OF EYES REPORTING INJECTION							
TOTAL REPORTS NEOVASC.							
NEOVASC. REPORTS > GR 2							
TOTAL NUMBER OF EYES REPORTING NEOVASCULARIZATION							
TOTAL VISITS							
TOTAL MISSED VISITS							

SHELF-LIFE PROTOCOL

Listed below is guidance for establishing, or extension of, shelf-life (expiration date) for sterile contact lens care solutions and tablets:

A. Manufacturing/Chemistry:

The manufacturer should demonstrate the stability of the solution or tablet over time as packaged and stored under the proposed storage conditions. Manufacturers should provide their shelf-life protocol and have shelf-life data sufficient to support their labeled expiration date prior to marketing their product.

The aging of the solution in the storage containers should be initiated as soon as possible. The stability tests should include all parameters (if applicable) such as pH, tonicity, viscosity, surface tension, active ingredients, and physical appearance. Accelerated aging up to 45°C may be used as supporting evidence of stability. Generally every 10°C increase for tested temperature will enhance the expiration date by a factor of two compared to the normal storage temperature. Containers selected randomly from a minimum of 3 lots are required for shelf-life tests for the smallest container size. Lot number, manufacturing date, testing date, and analytical methodology for the active ingredients should be provided. Note: Manufacturers may release product with shelf-life based initially on accelerated stability data. However, the shelf-life protocol should provide for ongoing "real-time" stability data to support the accelerated data.

The size of the container tested should be the same as that intended to be marketed. Generally, if the solution is susceptible to chemical degradation via light and oxygen, the greater the internal contact of the solution with the container surface the greater the chance of chemical degradation. The degradation, therefore, is more likely to occur in smaller containers because the ratio of solution volume to internal surface area decreases as the container size decreases. For this reason, DOD may grant 510(k) clearance of a solution in a container larger than that used for stability testing, but usually not a container smaller than tested unless additional testing is conducted by the sponsor according to cleared/approved protocol and product specifications remain unchanged. This policy may extend to containers eight times the size tested provided the containers are constructed of the same materials. Currently, the largest size container marketed is a 16 fl. oz. container.

B. Microbiology:

Manufacturers should demonstrate the preservative effectiveness or bacteriostasis and sterility for multi-dose packaged solutions to establish shelf-life. An approved extension of shelf-life protocol permits the manufacturer to extend shelf-life up to the time designated in the protocol without submitting a new 510(k). Preservative effectiveness (Micro--Appendix A) and bacteriostasis testing (Micro-Appendix C) are conducted, as applicable.

Maintenance of sterility over a product's shelf-life may be determined by USP sterility testing or by validated package integrity testing. If sterility testing is performed, product samples should be stored at

temperatures up to 37°C. These random samples should be from 3 lots of approximately the same age. The samples should be stored in a manner that maximally tests the container/closure system (e.g., inverted).

Shelf-life can be established using "real time" data from sterility and preservative effectiveness or bacteriostasis testing. Shelf-life based on "real time" data may be given a shelf-life equal to the time which packaged solutions are stored at ambient temperature (generally 23±2°C).

For example, samples stored at ambient temperature (generally 23±2°C) for 24 months may be granted a 24-month (2-year) expiration date if they have passed the microbiology stability testing and physical/chemical stability requirements outlined in the extension of shelf-life protocol.

Accelerated studies may be run for preservative effectiveness testing, bacteriostasis testing and validated package integrity testing at a maximum temperature of 45°C to establish shelf-life. Manufacturers should support the accelerated data with ongoing "real-time" data. Accelerated shelf-life estimates should be calculated using the following information:

1. Accelerated Storage Time refers to the actual storage time at elevated temperature for packaged solutions.
2. Acceleration Factor refers to the factor used to extrapolate the aging of the samples at the elevated temperature. The Acceleration Factor should be based on Q_{10} equal to 2.0 for each 10°C above ambient temperature.

Accelerated shelf-life estimates may be calculated as follows for samples stored only at the accelerated temperature:

Step 1. Calculate the Acceleration Factor based on the temperature difference between the elevated temperature and the ambient temperature. For example, based on a 15°C rise above ambient temperature, the Acceleration Factor may be calculated as $2.0^{(1.5)} = 2.83$; the Acceleration Factor based on a 20°C rise above ambient temperature is $2.0^{(2)} = 4.0$.

Step 2. Accelerated Storage Time x Acceleration Factor
= Accelerated Age or Shelf-life

For samples which are stored at ambient temperature prior to being stored at the elevated temperature, the age of the sample at the start of the accelerated study can be added to the Accelerated Age when calculating shelf-life.

A product may be marketed in a container up to 8 times larger than the container tested for shelf-life (identical container and closure system). Currently, the largest size container marketed is a 16 fl. oz. container. If a product is to be marketed in a container smaller than the container previously tested for shelf-life, the manufacturer should perform the applicable shelf-life testing.

Ordinarily, FDA will not require a 510(k) for extension of shelf-life beyond the shelf-life requested in the original 510(k) provided the same protocol is followed.

FDA will consider alternative methods to sterility testing to support package integrity provided a method is adequately validated.

For multi-dose preserved contact lens care products, the labeling and instructions for use may include a statement recommending the period for which a product should be used after opening (discard date). This recommended period should be based on container size, projected number of uses, and frequency of use, as determined by the manufacturer. For bacteriostatic solutions, a discard date should be determined according to the bacteriostasis test (Micro--Appendix C).

QUESTIONS AND ANSWERS

- Q1: Because this guidance document is the "special control" which is the basis for reclassification, am I required to conduct every test listed for a given product?
- A1: The term "special control" refers to a variety of items such as guidance documents or product specific labeling which are available to provide reasonable assurance of safety and effectiveness within the scope of Class II regulation of a medical device. As stated in the Introduction Section, Purpose of Document, this guidance provides comprehensive directions to manufacturers for collecting and preparing data for a 510(k). The preclinical and clinical testing is that which FDA believes to be acceptable to establish substantial equivalence. Persons may choose to follow the guidance, or may follow different data collection and preparation procedures. Alternative procedures will need to be justified to CDRH's satisfaction that they are applicable to demonstrate substantial equivalence. The specific scientific items listed in the guidance represent the minimum which should be addressed to demonstrate substantial equivalence. In some cases it may be possible to address the item without conducting or repeating the specific test.
- Q2: What is the difference between intended use and indication for use?
- A2: The intended use of a medical device is defined in 21 CFR 801.4 and guidance is provided in CDRH Blue Book Memorandum K86-3. It refers to how a product is to be used. The GUIDANCE FOR INDUSTRY--PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS includes a variety of product specific intended uses as exist in 1996 with current technology. An example of a product specific intended use is an in-eye lubricating drop. The indication for use is a specific statement which includes the intended use of the device. An indication for the in-eye drop may be limited to either hydrophobic (RGP) or hydrophilic (soft) lenses, or it may include both. If a product had been legally marketed for use with soft lenses only, and later a manufacturer wants to market it for both soft and RGP lenses, this would be a change in indication, but not a change in the intended use since the product specific use remains the same. A new 510(k) application is required for either a change in intended use or a change in indication.
- Q3: How do I use a product specific matrix for a "me-too" product, and for a product which isn't "me-too"?
- A3: The matrices are designed to provide guidance for products with the same active ingredients as the predicate device (so called "me-too products"), as well as products which contain different active ingredients, for the various product specific intended uses. When developing a product with the same active ingredient, a manufacturer determines the concentration of the active ingredient in the formulation then refers to the appropriate column for guidance. Recommended testing may vary depending on whether the active ingredient is formulated at a higher, lower, or the same concentration as the predicate device. When a manufacturer develops a

formulation which contains a different active ingredient from the chosen predicate device, or when the active ingredients are new for ophthalmic use, the fourth column is provided for guidance.

- Q4: Why is a "new ingredient for ophthalmic use" grouped in the same matrix column as a "different active ingredient" for a given product specific intended use?"
- A4: As stated in Section II., General Manufacturing Information, the guidance focuses primarily on active ingredients. The active ingredient a manufacturer chooses to use to achieve the product specific intended use, (e.g. cleaner, disinfecting product, etc.) will often be the same active ingredient as found in the predicate device. Additional testing is recommended when the manufacturer uses a different active ingredient than found in the predicate device since that case generally represents the need for additional information to determine substantial equivalence.
- Q5: What are the different hydrophilic and rigid gas permeable (RGP) lens groups and why are tests conducted with representative groups?
- A5: The lens groups are described in detail in the PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR DAILY WEAR CONTACT LENSES. There are four hydrophilic groups based on ionic surface charge and water content (Groups I, II, III, and IV). There are also four RGP groups based on material composition. However, the majority of currently marketed RGP lenses fall into only two of the four groups; silicone acrylate and fluorosilicone acrylate. The pure fluoropolymer group consists of only one polymer which currently is not marketed, and the last group represents an assortment of RGP materials which are generally no longer marketed or rarely encountered. It is primarily the solution manufacturer's responsibility, not the lens manufacturer's, to demonstrate compatibility with the indicated lens material groups.
- Q6: If my product is already approved for use with a soft lens, do I have to do any testing to change the indication to include use with RGP lenses, or may I just revise the labeling as necessary? What about the reverse situation (i.e. going from RGP to soft lens use)?
- A6: In either case, a new 510(k) will be necessary, although the content may differ. Soft lens use may be a worst case in some situations, so the recommended tests in the product specific matrix need to be considered and addressed individually. A solution for RGP lenses may prove to be incompatible with soft lenses due to lens absorption or adsorption of an ingredient. Because the manufacturer should know the product very well, characteristics of the active and inactive ingredients will dictate whether toxicology screening needs to be repeated, or if preservative uptake studies are necessary. The guidance is designed to rely on preclinical testing to answer the major part of the compatibility question. The characteristics of the product, along with the indication change, will dictate how much or how little testing is necessary and which areas may be addressed by explanation.
- Q7: Why are contact lens solutions intended for chemical disinfection of lenses not generally labeled as "chemical disinfectants"?

- A7. The distinction is made to differentiate contact lens disinfecting solutions from more potent chemical disinfectants used to prevent patient to patient transmission of microorganisms both on medical devices which are disinfected between patients, and on inanimate surfaces. The term "chemical disinfectant" generally applies to germicidal products demonstrating a six log reduction in microorganisms using Association of Official Analytical Chemists (AOAC) test methods. Historically contact lens solutions intended to destroy ocular pathogens have been labeled as disinfecting solutions, even though many products do not meet the same efficacy criteria as other chemical germicides. The lower recommended efficacy criteria outlined in this guidance document for contact lens disinfecting solutions are intended to minimize the risks of toxicity to ocular tissue from the contact lens care solutions while providing a regimen for effective reprocessing of contact lenses.
- Q8: What is the difference between a "chemical disinfecting solution" and a "chemical disinfection system"?
- A8: As defined in Micro--Appendix B, Disinfection Efficacy Testing, there are two levels of antimicrobial efficacy with performance criteria modeled after the ISO/CEN draft requirements. For both levels, cleaning is an integral part of the lens care process necessary to achieve proper lens care. A product may be labeled as "disinfecting solution" only when it meets the higher level of antimicrobial efficacy for the "Stand-Alone" test. The "Regimen" procedure evaluates the adequacy of the entire "chemical disinfection system for solutions which fail to meet the Stand-Alone efficacy criteria."
- Q9: If I want to change my bottle size or the material the bottle is made from, do I need to submit a new 510(k)?
- A9: In Section IV. Modifications of Approved Contact Lens Care Products requiring a 510(k), this question is addressed under Section B., examples which should not require a 510(k). As stated in the Shelf-Life Protocol Appendix, there can be greater chemical degradation in susceptible solutions when the container size is decreased since the ratio of solution volume to internal surface is decreased. For that reason, stability test data are necessary to establish a shelf-life for the smallest container. A new 510(k) should not be necessary provided the testing performed demonstrates that the product specifications remain unchanged and proper documentation is included in the device master record. Likewise, a change in packaging material should not be necessary provided the conditions noted in Section IV.B.4. are met. This packaging change guidance is a continuation of a policy in place while these products were regulated under Class III. At that time packaging changes meeting specified criteria were reportable in the Annual Report to the PMA rather than under a PMA supplement.
- Q10: The Toxicology Appendix lists three minimum recommended toxicology tests under Section II., but the Acute Oral Toxicity is not recommended in all cases in the product specific matrices. What is really necessary?
- A10: This is generally addressed as a labeling precaution when appropriate. If a predicate device with the same active ingredient is used, the predicate device labeling would already address this item. If a new active

ingredient is used, information on oral toxicity may already be available, so the test may not have to be actually conducted to address this item.

Q11: The statement "when clinical performance data are necessary" is somehow tied into the "physical/chemical, microbiological and toxicological data to support a claim." What does this really mean?

A11: The guidance really emphasizes preclinical testing. In many cases, a side-by-side analysis with the predicate device will go a long way to demonstrating substantial equivalence. The tests and parameters noted in Section II. General Manufacturing Information introductory paragraph and Section A, and in Section IV. Modifications of Approved Products A.1 list the primary physical/chemical preclinical comparisons. When these test data demonstrate a difference from the predicate device, additional clinical performance data are recommended.

Q12: With so many options for controls in clinical design, how do I decide which one to choose?

A12: In general, the complexity of the study design will reflect the uniqueness of the product. For example, a clinical study of a "me-too" product with the same active ingredients may be addressed without a concurrent control. If the product has different active ingredients from the predicate device, but does not contain a new ingredient for ophthalmic use, then a control group would be appropriate. When the new ingredient is also a new ingredient for ophthalmic use, randomization may be appropriate.

Q13: Do I need 510(k) clearance for separate instructions to practitioners for in-office disinfection?

A13: Yes. The additional 510(k) clearance pertains to specific instructions the manufacturer may want to develop for in-office disinfection of trial lenses. Refer to Section III. C. Chemical Disinfecting Products for current labeling and test recommendations intended to address the additional safety considerations associated with trial lens disinfection between patients.

Q14: Can I add catchy statements to my product's labeling to give it a marketing edge?

A14: When developing product labeling, the manufacturer should refer to the predicate device labeling for the product specific intended use and directions for use. The manufacturer has the responsibility for familiarity with applicable regulations to avoid misbranding his or her device. A determination of substantial equivalency will be based on the predicate device's labeling, as well as the product specific intended use and directions for use. FDA primarily reviews medical device claims which concern the safety and/or effectiveness of the device as well as those which address inherent properties of the device. Manufacturers should be aware that additional product attribute labeling claims such as comparative claims to another manufacturer's product will usually require significant data above the minimum necessary information recommended in the GUIDANCE FOR INDUSTRY--PREMARKET NOTIFICATION (510(k)) GUIDANCE DOCUMENT FOR CONTACT LENS CARE PRODUCTS to determine substantial equivalency.

- Q15: Why do I have to use all those boxes in my labeling from that Write-it-Right example? There's no regulation that says I have to do it that way.
- A15: Yes, you are correct. There are no specific regulations concerning this model. The Write-it-Right example is included for the benefit of those manufacturers who wish to utilize that labeling model. The Write-it-Right booklet referenced is available from CDRH/DSMA. If a manufacturer uses that model, it is recommended that the concepts be followed, or a justification and explanation be provided for deviations from the model. For example, Write-it Right suggests that the labeling be geared to a seventh grade reading level. If a different reading level is used, an explanation should be provided.
- Q16: Why do I need to submit a new 510(k) if I want to have my saline solution used as a rewetting agent? Do I really need a clinical study for something like that?
- A16: These two questions involve more than one answer. If the saline product is already cleared for marketing, then it certainly would be possible to address the clinical study issue. Remember back to the first question? Not every test needs to be conducted if it can be adequately addressed. It's very difficult to write a guidance to clearly direct a manufacturer to each possible situation. The matrices are mainly constructed to provide guidance for a new manufacturer of a new product. In that situation, there's nothing to establish the biocompatibility of a product, even if it's a "me-too" product. That's why the toxicology screening tests are listed in the matrix. Because manufacturing processes and inactive ingredients may vary, there need to be some data to support biocompatibility, either toxicology and/or clinical data. The matrices are also to be used for guidance when legally marketed products are modified. In that situation, some of the test data already available may be applicable to address a specific item.
- As for the need for a new 510(k), the change in labeling is a new indication for use of the saline and requires a 510(k). In addition, both Sections III. D. Multi-purpose Solution and E. In-eye Contact Lens Solutions address issues related to current policy for in-eye products. In order to both reduce the risk of contamination during use and to facilitate ease of use, lubricating and rewetting solutions should be packaged in bottle sizes not to exceed 30 ml. FDA believes that limiting the indications for in-eye use solutions to a single intended use (even when the chemical composition is identical to a multi-purpose solution, saline or conditioning solution) enhances product safety and encourages consumer compliance with safe lens care practices.

End of Guidance

EXHIBIT Z

(Exhibit 2)

January 30, 2017

Page 1

IN THE CIRCUIT COURT OF THE 17TH JUDICIAL CIRCUIT IN AND
FOR BROWARD COUNTY, FLORIDA

CASE NO.: CACE-15-008373

CLARE AUSTIN,
Plaintiff,

vs.

C.R. BARD, INC., a foreign corporation
and BARD PERIPHERAL VASCULAR, INC.,
an Arizona corporation, et al.

Defendants.

_____ /

TRANSCRIPT OF HEARING PROCEEDINGS

VOLUME 1 (Pages 1 - 144)

DATE TAKEN: January 30, 2017

TIME: 9:00 a.m.

PLACE: Broward County Courthouse
201 Southeast 6th Street, Courtroom 850
Fort Lauderdale, Florida

BEFORE: John J. Murphy, III, Circuit Judge

This cause came on to be heard at the time and
place aforesaid, when and where the following
proceedings were stenographically reported by:

Thomas N. Sevier, FPR

January 30, 2017

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1 what is the state law involving the duty of a
2 company, not whether or not they've gone through
3 this 510(k) process.

4 So that's coming later, Your Honor. We'll
5 talk in more detail about that.

6 THE COURT: Thank you. I look forward to it.
7 So, Counsel, we can start with your motions.

8 MR. GERECKE: Yes, Your Honor. Thank you.

9 THE COURT: We're going to start with the
10 plaintiff's motions.

11 MR. LOPEZ: We have to shuffle the deck here.

12 MR. JOHNSON: Plaintiff has one motion for
13 summary judgment. It relates to an affirmative
14 defense asserted by Bard. It's a statutory defense
15 based on Florida Statutes 768.1256. That is what
16 we refer to as the government rules defense.

17 I'm going to summarize that statute. But yet
18 creates a rebuttable presumption in a product
19 liability claim that a product or device is not
20 defective or unreasonably dangerous if there are
21 three elements that are met.

22 And the element that we are raising with the
23 Court for our contention that this affirmative
24 defense doesn't apply is paragraph B; which says
25 that codes, statutes, rules, regulations or

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1 standards that are designed to prevent the type of
2 harm that allegedly occurred would be one of the
3 elements that would entitle Bard in this case to a
4 government rules defense.

5 That subparagraph B invokes the 510(k)
6 process, which is how this device made its way to
7 market. And as I mentioned during my brief
8 opening, that is a clearance process. It is not an
9 approval by the FDA that a device is, in fact, safe
10 or effective. It is not what that statute or that
11 regulation is designed to do.

12 Safety is not the purpose of that regulation.
13 Equivalence is the purpose of that regulation. And
14 it requires Bard when it submits its application
15 for clearance to honorably tell the FDA that this
16 device is, in fact, the equivalent to an existing
17 device, the Recovery filter in this case. That
18 obligation continues after the device makes it way
19 to market.

20 We have cited in our briefing to the court the
21 Medtronic versus Lohr case. That is a United
22 States Supreme Court case. And it stands for the
23 proposition that the 510(k) process is focused on
24 equivalence, not safety.

25 There was an amicus brief that was filed by

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1 the FDA -- I don't know if it was in Medtronic or
2 another case, but it's cited in our brief -- which
3 also establishes from the mouth of the FDA that the
4 510(k) process is not a safety regulation, it is
5 geared toward equivalence.

6 And then there were two fairly recent cases
7 out of West Virginia. One is the Lewis case, Lewis
8 versus Johnson & Johnson. The other one is
9 Edenfield versus Boston Scientific. The Edenfield
10 case actually interpreted the Florida Statute
11 that's in question right now. And that involved
12 another product liability claim against a device
13 manufacturer.

14 Bard was also involved in that MDL out of West
15 Virginia. And the court in West Virginia
16 specifically held that a medical product liability
17 claim where the device is cleared through the
18 510(k) notification process, the government rules
19 defense, 768.1256, is not a defense under those
20 circumstances because the purpose of that
21 regulation is not safety. The purpose is
22 equivalence.

23 And there's no doubt that this 510(k) process
24 does have some safety features to it. But that is
25 not the primary purpose of that regulation, which

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1 is why this government rules defense does not apply
2 in this case.

3 THE COURT: Thank you.

4 MR. GERECKE: Your Honor, the government rules
5 defense has three elements. And the plaintiffs are
6 not challenging two of the elements. The only
7 element they're challenging is subsection B; which
8 says the codes, statutes, rules, regulations, or
9 standards are designed to prevent the type of harm
10 that allegedly occurred. So that's the element
11 they're challenging on summary judgment.

12 And their argument is that the 510(k)
13 clearance process is not a safety regulation, has
14 nothing to do with safety. On summary judgment
15 there are issues of fact that would preclude entry
16 of summary judgment on that defense. We've cited
17 them in our memo.

18 I would like to read from two of these
19 documents that we have filed, which create an issue
20 of fact as to whether or not the process involves
21 health. One is a publication, the CDRH Preliminary
22 Internal Evaluations from the 510(k) working group
23 in August of 2010 out of the Center for Devices and
24 Radiological Health of the U.S. Food and Drug
25 Administration on page 34.

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1 It says, As described above, the 510(k)
2 program has changed significantly since its
3 inception. The MDA established the premarket
4 notification process as a simple check to assure
5 proper device classification.

6 And it goes on to say importantly, Through
7 various statutory regulatory modifications over
8 time, it has become a multi-faceted premarket
9 review process that is expected to assure that
10 clear devices, subject to general and applicable
11 special controls, provide reasonable assurance of
12 safety and effectiveness and to facilitate
13 innovation in the medical device industry, speaking
14 specifically to the assurance of safety and
15 effectiveness.

16 There's a publication that we cite and filed,
17 Your Honor, from 2014. The 510(k) program
18 evaluating substantial equivalence of premarket
19 notifications out of the FDA -- on page 6 -- when
20 it talks about the 510(k) review standard, the
21 statutory standard, it says 510(k) review
22 standard -- and then they describe it -- and it
23 says, The 510(k) review standard is comparative;
24 whereas the PMA standard relies on an independent
25 demonstration of safety and effectiveness.

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1 Nonetheless, the principles of safety and
2 effectiveness underlie the substantial equivalence
3 determination in every 510(k) review. This is a
4 2014 publication of the FDA stating that every
5 single 510(k) review involves principles of safety
6 and effectiveness underlying the determination of
7 each one.

8 There was a very recent publication out of the
9 FDA just ten days ago entitled -- we wanted to get
10 this and also file it -- Public Health Interest and
11 First Amendment Considerations Related to
12 Manufacturer Communications Regarding Unapproved
13 Uses of Approved or Cleared Medical Products, which
14 says the same thing in that publication.

15 Your Honor, we're here on a summary judgment
16 motion. As Your Honor well knows, if there's any
17 issue of material fact, a summary judgment can't be
18 granted. We have filed materials disputing the
19 underlying fact they say is indisputable and it's
20 not. The publications of the FDA tell us that
21 safety and effectiveness underlie the 510(k)
22 process. So on that ground alone there is an issue
23 of fact, and the summary judgment can't be granted.

24 Frankly, this is an issue, Judge, that is
25 going to be ferreted out at trial. You know, the

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1 charge conference we're going to decide what
2 instructions go to the jury. And that's the
3 appropriate time to deal with something like the
4 government rules defense, and certainly not on the
5 summary judgment when we have created an issue of
6 fact for the record.

7 THE COURT: Thank you. Anything else?

8 MR. JOHNSON: Judge, real brief. There are
9 two pathways to get a device in the market and used
10 in the real world.

11 One is the PMA process, which defense counsel
12 spoke to. That is a very rigorous process that
13 requires a manufacturer to perform clinical studies
14 to demonstrate to the FDA that a device is, in
15 fact, safe. And in that instance, the FDA will
16 approve that device and determine that it is safe
17 for use in the real world.

18 When a manufacturer uses the 510(k) process --
19 and I am going to quote from a GAO report regarding
20 medical devices shortcomings in FDA premarket
21 review. It talks about the 510(k) process. And it
22 is the less stringent way to get a device to
23 market. And when these submissions occur, the
24 clinical data are not required and substantial
25 equivalence would normally be determined based on

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1 comparative device descriptions.

2 The point is that when the 510(k) process is
3 used -- I mean, I think it would be silly for me to
4 tell the Court that there are no safety features to
5 that process. There are. But the issue in this
6 case is whether that process is established to
7 prevent the type of harm that occurred here. Lohr
8 says it's not. The Lewis case out of West Virginia
9 says it's not.

10 And the District Court judge in West Virginia
11 in deciding this issue in Edenfield in October of
12 2015 said that the 510(k) process is not designed
13 to prevent the type of harm caused when a medical
14 device is cleared for use in the real world. And
15 there's a huge difference between approval and
16 clearance. And this is a clear device.

17 And the foundation for clearance is that a
18 device manufacturer abide by the honor code, and
19 they're not supposed to make application when they
20 know that their device is not the substantial
21 equivalent to a predicate or an existing device.
22 And when a device manufacturer doesn't abide by
23 that honor code, things happen that are bad, as
24 happened to Clare Austin in this case.

25 This is not a safety process. And it's for

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1 that reason summary judgment should be granted.
2 There are no issues of material fact in this case.
3 This is a pure question of law that the Court
4 should and will need to decide.

5 THE COURT: Thank you.

6 Yes, sir. Something else?

7 MR. GERECKE: No.

8 THE COURT: What's next? I'm going to defer
9 ruling on it.

10 MR. JOHNSON: Judge, the next motion for
11 summary judgment is defendant's motions.

12 MR. GERECKE: Yes.

13 THE COURT: Which motion, Counsel? Which
14 motion do you want to start with?

15 MR. GERECKE: We have Bard's motion for
16 partial summary judgment, which with the
17 plaintiff's withdrawal of a number of their claims
18 is limited to the warnings claim and the punitive
19 damages claim.

20 THE COURT: Do you know which binder it's in,
21 Counsel?

22 MR. JOHNSON: Judge, that would be part of a
23 five set of binders. That should be one of five.
24 Judge, I can probably locate an extra copy, if
25 you'd like.

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1 COURT CERTIFICATE

2

3

4 STATE OF FLORIDA

5 COUNTY OF BROWARD

6

7 I, THOMAS N. SEVIER, Florida Professional
8 Reporter, certify that I was authorized to and did
9 stenographically report the foregoing proceedings
10 and that the transcript is a true and complete
11 record of my stenographic notes.

12

13 Dated this 13th day of February, 2017.

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THOMAS N. SEVIER, FPR

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